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HISTOLOGIC ATLAS OF GLIOMAS*

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BOSTON

This atlas was prepared in answer to a demand for illustrations of specimens of the different types of gliomas made from preparations stained with the ordinary methods used in pathologic laboratories. Since the diagnosis of tumors as usually practiced is largely a matter of matching, the demand seemed legitimate. There are many difficulties in the preparation of such an atlas, not the least of which is that of choosing the illustrations, for the number of plates must be limited. This limitation is unfortunate because no two gliomas are alike. The gliomas do not fall into distinct groups in which all the members look alike, but consist of variant individuals with certain family resemblances. To find a typical member of each family with which the others may be recognized on comparison is about as difficult as to find a typical member of the Alpine or Dinaric races.

However, the attempt has been made. The plan adopted has been to present the type at two different and constant magnifications in photomicrographs taken from sections stained with hematoxylin and eosin. In case there is great variation in the architecture of any group, variants are shown. Details of structure are given at any convenient magnification from preparations made by special methods. The photographs have not been retouched.

The classification or grouping adopted in this atlas is that detailed recently,[1] and is a simplification of the classification prepared by Dr. Cushing and me.[2]

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* From the Surgical Clinic of Dr. Harvey Cushing, Peter Bent Brigham Hospital.

1. Bailey: Bull. Johns Hopkins Hosp. **40**:354, 1927.

2. Bailey and Cushing: Tumors of the Glioma Group, Philadelphia, J. B. Lippincott Company, 1926.

Explanation of Plate I

HISTOGENESIS

This plate presents in diagrammatic form the histogenesis of the central nervous system, accurate knowledge of which constitutes the essential background for a clear understanding of the tumors of the brain substance, known in general as gliomas. Unfortunately, knowledge of the development of the brain is incomplete, and the details of this development vary in different parts of the nervous system, so that the diagram is partly hypothetic.

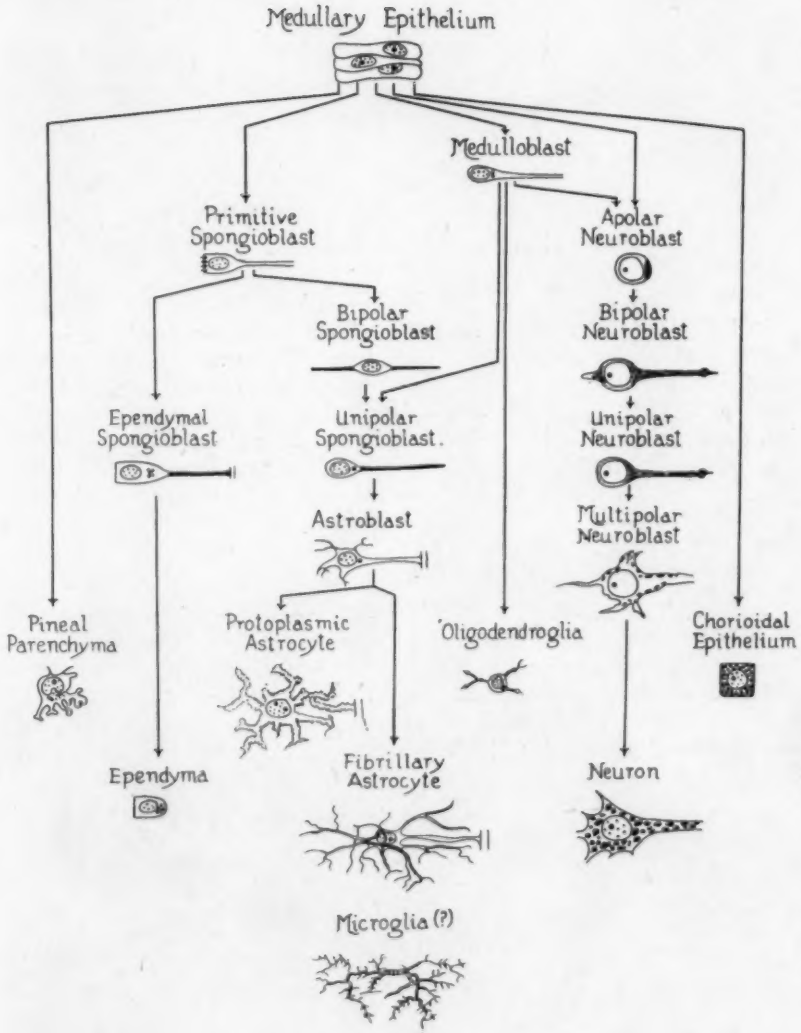
Especially hypothetic are the medulloblasts, described by Schaper under the apt term of "indifferenten Zellen," for they do not have morphologic characteristics by which they may be identified. Yet the hypothesis of their existence seems to be necessary to explain the histogenesis of the nervous system, its malformations and its tumors.

The exact derivation of the microglial cells is unknown. Hortega considers them to be of mesodermal origin, but his views have not gone unchallenged (Pruijs); it is possible that they may be derived, like the oligodendroglia, through the medulloblasts, although the fact that they do not take a part in the formation of gliomas seems strange if they have a common origin from the medullary ectoderm.

It will be seen in the following pages that certain of these cellular types predominate in certain tumors, and Dr. Cushing and I have shown that those tumors composed of more embryonic cells have a shorter clinical course.

(For a description of the histogenesis of the nervous system, see Bailey and Cushing, footnote 2, pp. 4-22).

PLATE I


Medullary Epithelium
Medulloblast
Primitive Spongioblast
Apolar Neuroblast
Bipolar Spongioblast
Bipolar Neuroblast
Ependymal Spongioblast
Unipolar Spongioblast.
Unipolar Neuroblast
Astroblast
Multipolar Neuroblast
Pineal Parenchyma
Protoplasmic Astrocyte
Oligodendroglia
Chorioidal Epithelium
Ependyma
Fibrillary Astrocyte
Neuron
Microglia (?)

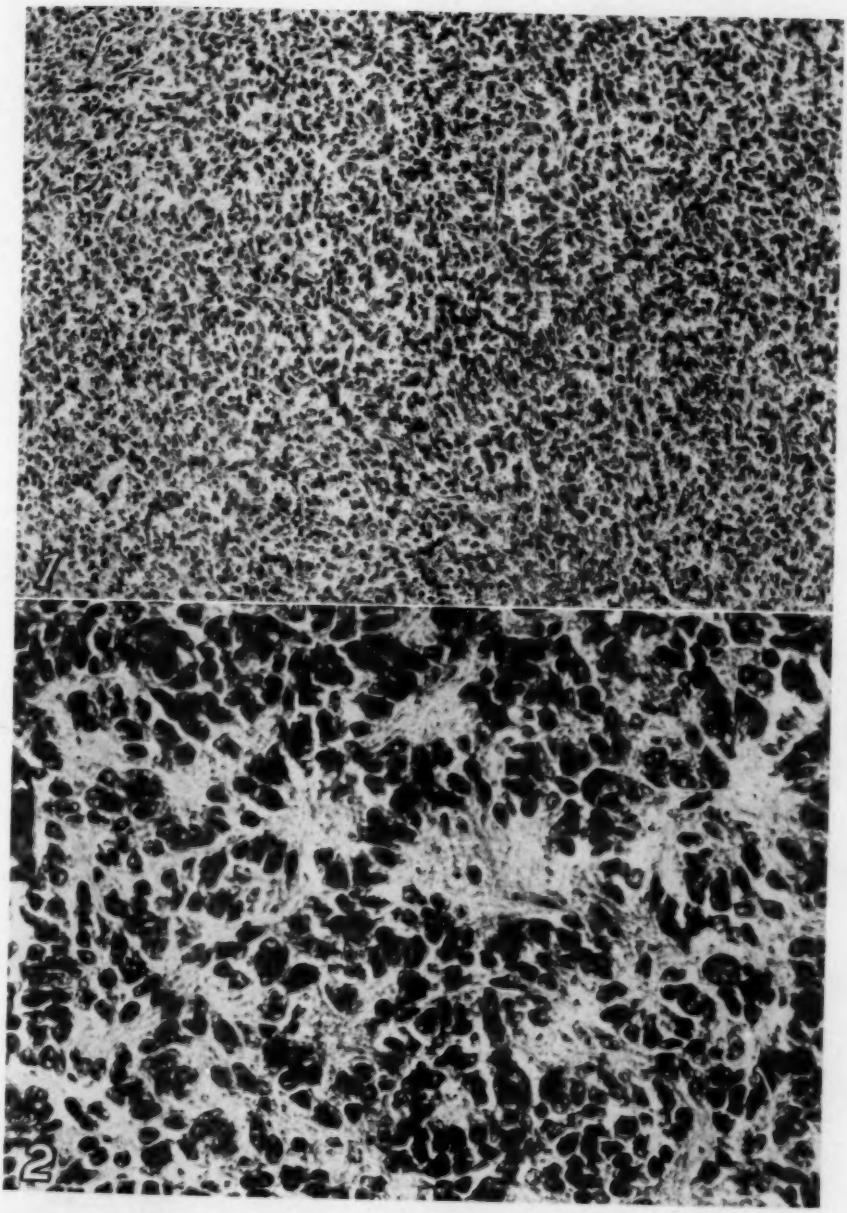
Explanation of Plate II

MEDULLOBLASTOMA

Fig. 1 (P. B. B. H., Path. no. N-22-31).—The component cells of the medulloblastoma for the most part do not have morphologic characteristics that can be sharply displayed by special staining methods. The diagnosis is aided by the differentiation of certain of the neoplastic cells into neuroblasts or into spongioblasts, sometimes both. With the hematoxylin and eosin stain, the diagnosis must often be based on architectural characteristics. Note here especially the numerous capillaries and the grouping of the nuclei so as to leave spaces filled with a delicate fibrillary material. Sometimes sprouts of reticular tissue pass between the capillaries, forming a stroma (plate IV, fig. 1) as first recognized by Wolbach. Methylene blue and eosin stain; × 100.

Fig. 2 (P. B. B. H., Path. no. N-22-80).—The grouping of the nuclei is seen here to better advantage. Many mitotic figures are present. These tumors are often described in the literature as sarcomas. They were called neuroblastomas by Wright. Borst would doubtless label them glioma sarcomatodes, and Masson described a typical tumor under the name of neurogliocytome embryonnaire. Hematoxylin and eosin stain; × 300.

PLATE II



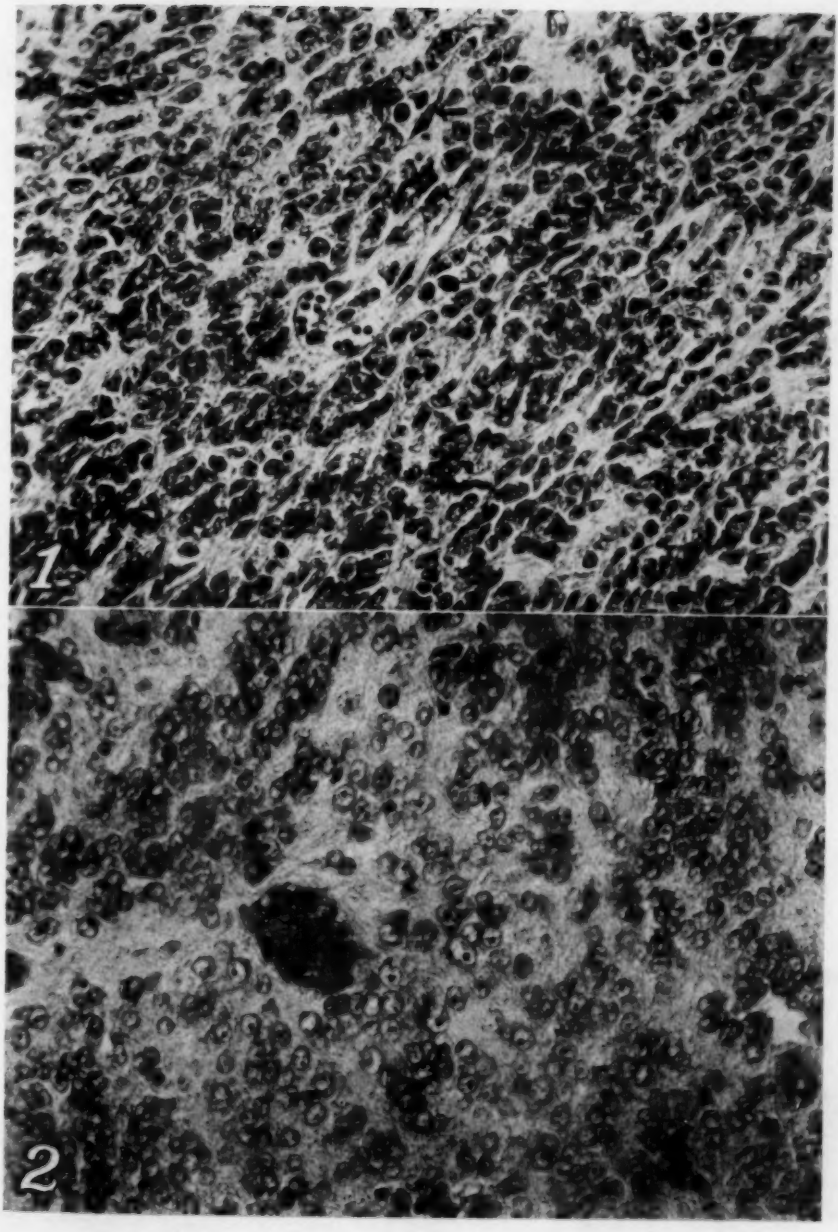
Explanation of Plate III

MEDULLOBLASTOMA

Fig. 1 (P. B. B. H., Path. no. N-21-113).—The clear areas filled with fibrillary material are not always so evident as in plate II; this is especially true when the neoplastic cells have a tendency to differentiate into spongioblasts, as in this illustration. It was tumors of this type that Dr. Cushing and I proposed to call spongioblastoma indifferentiale. One bipolar spongioblast is indicated by the arrow; many others are present (plate V, fig. 2). Hematoxylin and eosin stain; × 300. (For other illustrations, see Bailey and Cushing, Arch. Neurol. & Psychiat. **14**:192 [Aug.] 1925.)

Fig. 2 (P. B. B. H., Path. no. N-25-55).—In this area, numerous neuroblasts are differentiating. They can be recognized in simple nuclear stains by their spherical vesicular nuclei, each with a heavy nucleolus, but are much more easily identified by special staining methods. One might possibly be justified in calling such a tumor in which neuroblasts are so numerous a neuroblastoma. Methylene blue and eosin stain; × 300.

PLATE III



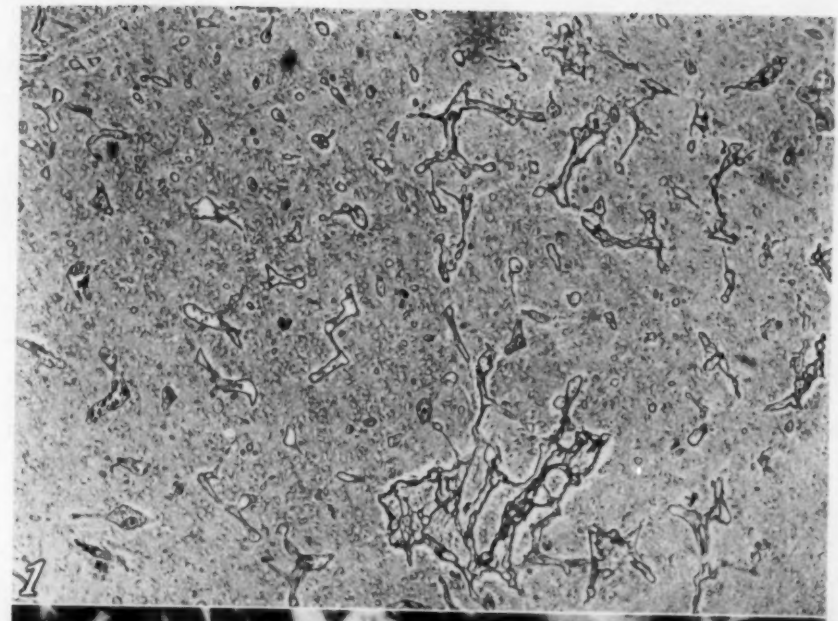
Explanation of Plate IV

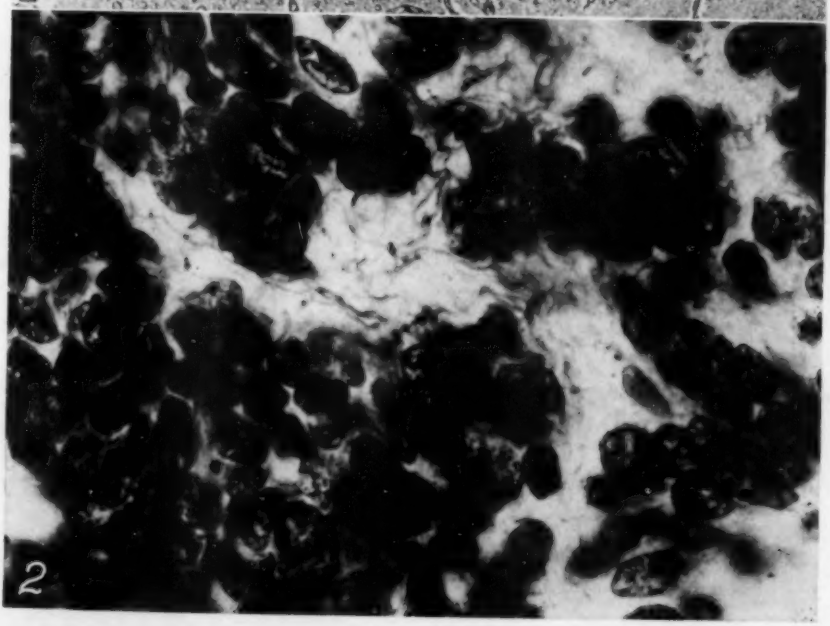
MEDULLOBLASTOMA

Fig. 1 (P. B. B. H., Path. no. N-22-80).—There are often numerous capillaries in these tumors, and the delicate reticular threads which pass between them may, in rare instances, be so numerous as to form a veritable spider's web. This illustration shows an average arrangement. Perdrau's ammoniacal silver method; × 80.

Fig. 2 (P. B. B. H., Path. no. N-21-113).—The delicate fibrillary material in these tumors occasionally contains neuroglial fibrils as shown in this illustration, sometimes unmyelinated nerve fibers (plate V, fig. 1), but for the most part it consists of delicate cytoplasmic strands which cannot be sharply stained or impregnated by any method. Neutral ethyl violet-orange G; × 850.

PLATE IV


1


2

EXPLANATION OF PLATE V

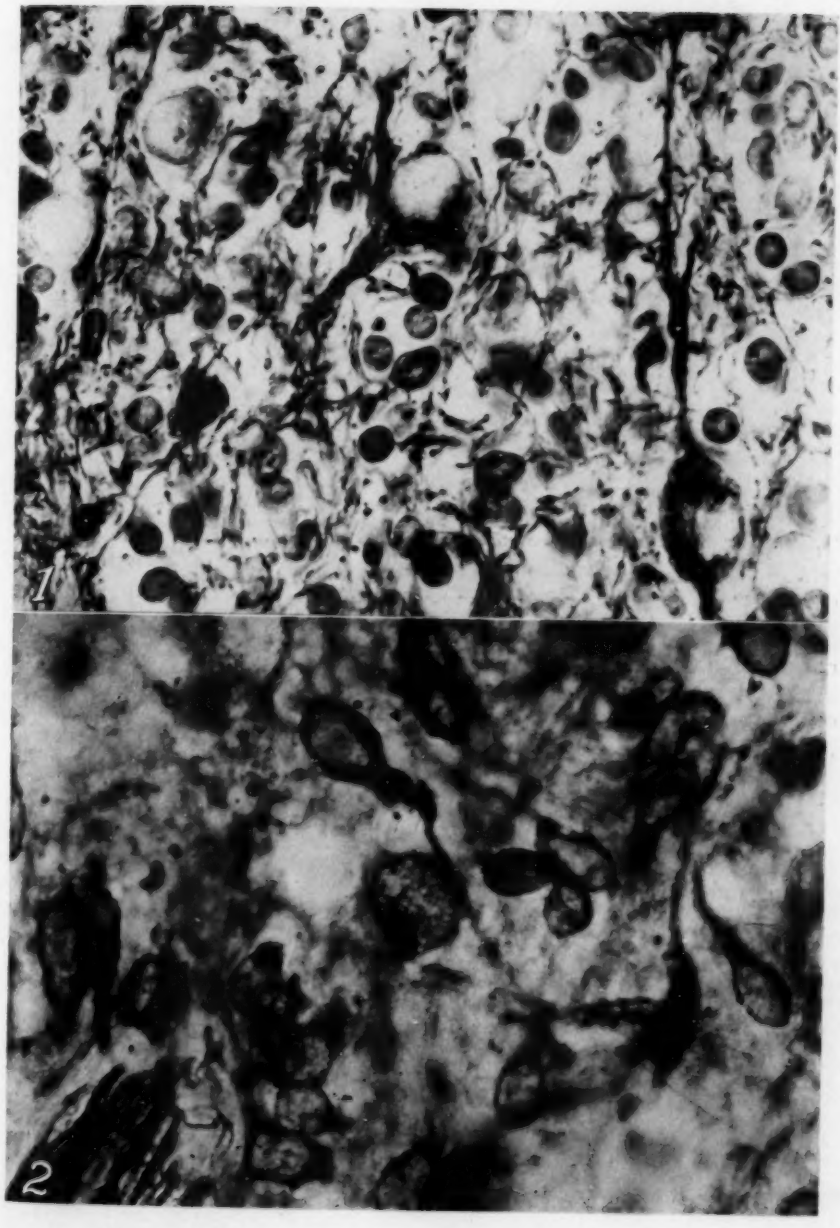
MEDULLOBLASTOMA

Fig. 1 (P. B. B. H., Path. no. N-25-100).—All the stages in the development of the neuroblast are displayed here. The first indication of the differentiation of a neuroblast is seen in the swelling of the nucleus. Then silver begins to be deposited in one extremity of the cytoplasm (fibrillogenous zone of Held), after which processes containing neurofibrils are pushed out from one or both poles. Cajal's reduced silver method; × 850. (Reproduced by permission of the Williams and Wilkins Company.)

Fig. 2 (P. B. B. H., Path. no. A-15-18).—The transformation of medulloblasts into unipolar spongioblasts is clearly seen. The cytoplasm only is impregnated, which brings into relief their tadpole-like shape. At the base of the tail of one of them, the centrosome is seen in the form of a heavy granule surrounded by a clear zone. Perdrau's ammoniacal silver method (modified); × 1,250.

(The group of medulloblastomas could be subdivided on histologic grounds depending on the predominance of neuroblasts, spongioblasts and stroma, but there would seem to be little practical advantage in doing so, for their behavior is very similar.)

PLATE V



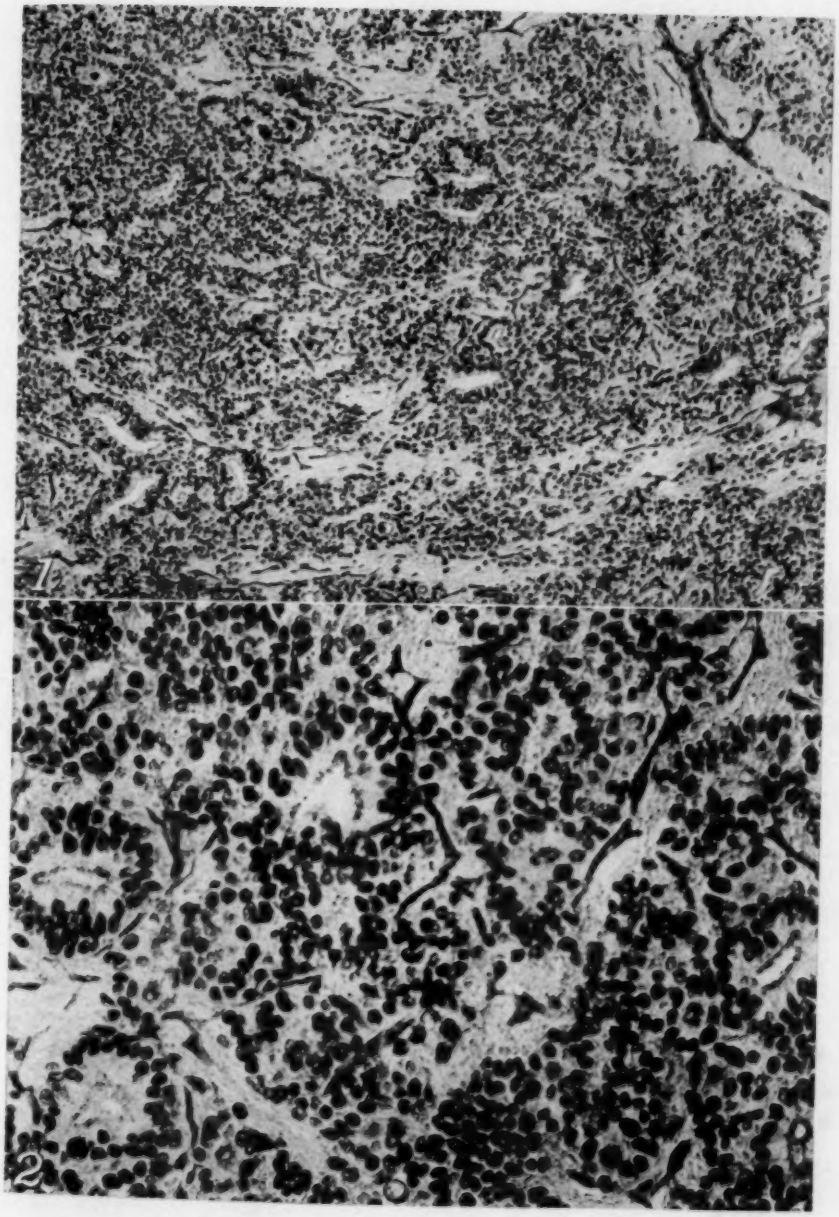
Explanation of Plate VI

NEURO-EPITHELIOMA

Fig. 1 (P. B. B. H., Path. no. NA-21-25).—The neuro-epithelioma is characterized by the presence of true rosettes, the cavities of which are surrounded by the epithelial bodies of primitive spongioblasts. These rosettes are well demonstrated by this section. Hematoxylin and eosin; × 100.

Fig. 2 (P. B. B. H., Path. no. NA-21-25).—The rosettes are shown at a higher magnification. The intervening tissue is much like that of a medulloblastoma. Such tumors are sometimes called blastoma ependymale (Marburg) or neuro-epithelioma gliomatosum microcysticum (Rosenthal). Hematoxylin and eosin; × 300.

Plate VI



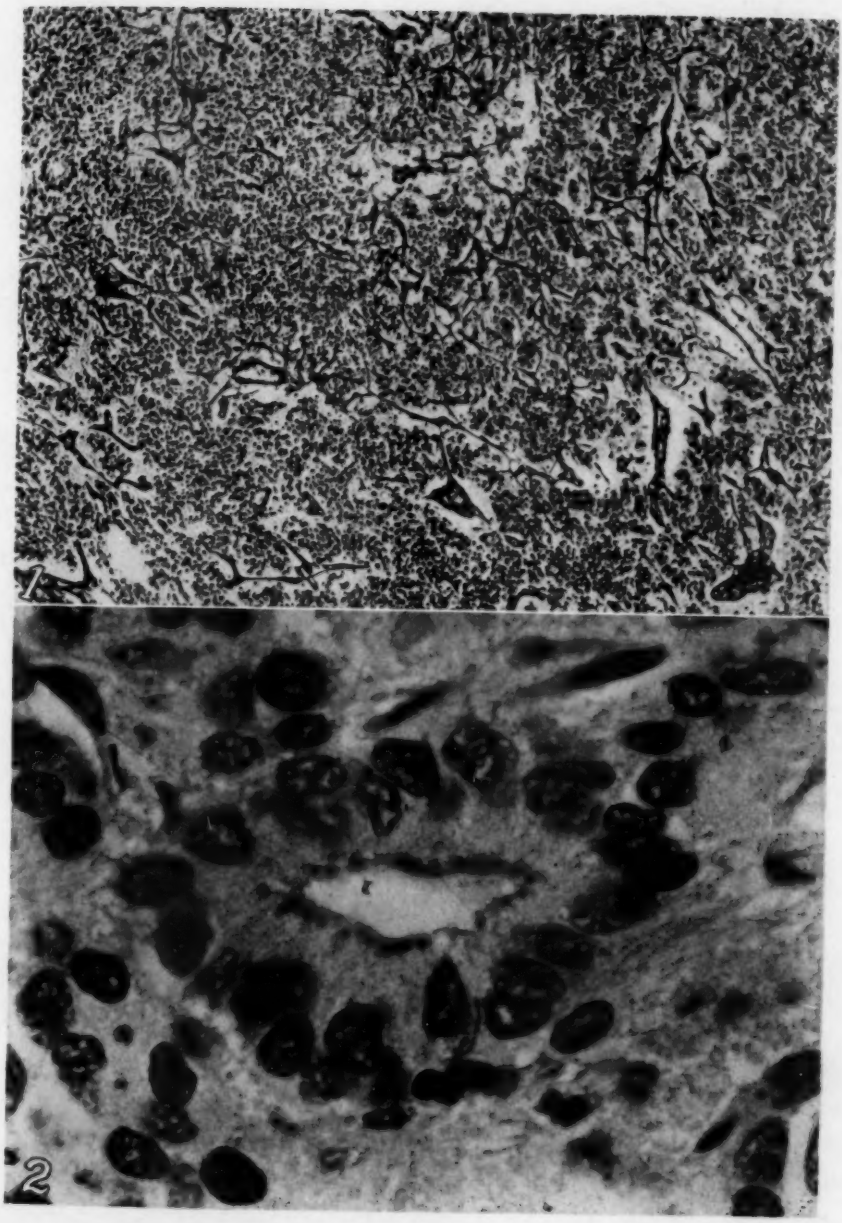
Explanation of Plate VII

NEURO-EPITHELIOMA

Fig. 1 (P. B. B. H., Path. no. NA-21-25).—An abundant network of reticulin is found, consisting of delicate strands passing between the small blood vessels. Achúcarro's tannic silver method; × 80.

Fig. 2 (P. B. B. H., Path. no. NA-21-25).—Note the blepharoplasten at the inner ends of the primitive spongioblasts of the rosette. There were probably also cilia, but the specimen was obtained so long post mortem that they are no longer demonstrable. Neutral ethyl violet-orange G; × 1,000. (Reproduced by courtesy of the J. B. Lippincott Company.)

PLATE VII



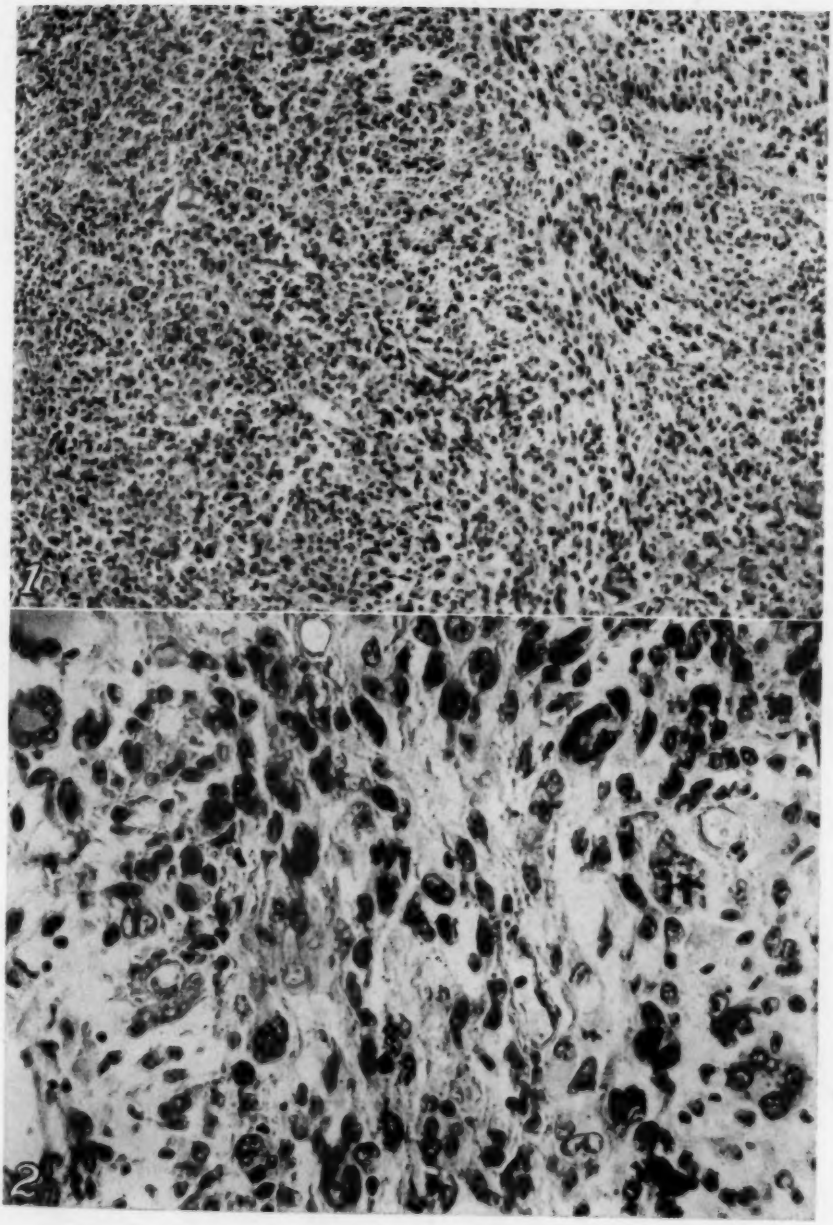
Explanation of Plate VIII

SPONGIOBLASTOMA MULTIFORME

Fig. 1 (P. B. B. H., Path. no. N-24-52).—The term spongioblastoma multiforme was first used for this tumor by Globus and Strauss. Often, as in this section, it bears a superficial resemblance to that of a spindle cell sarcoma, hence the name gliosarcoma is often applied to it. Hematoxylin and eosin; × 100.

Fig. 2 (P. B. B. H., Path. no. N-24-52).—Examination at a higher magnification always reveals numerous mitoses, true tumor giant cells and an intercellular fibrillary material consisting of the frayed-out ends of the spindle-shaped cells. Because of the variation in cellular structure, these tumors were described by Roussy, Lhermitte and Cornil as gliomes polymorphes. Hematoxylin and eosin; × 300.

PLATE VIII



Explanation of Plate IX

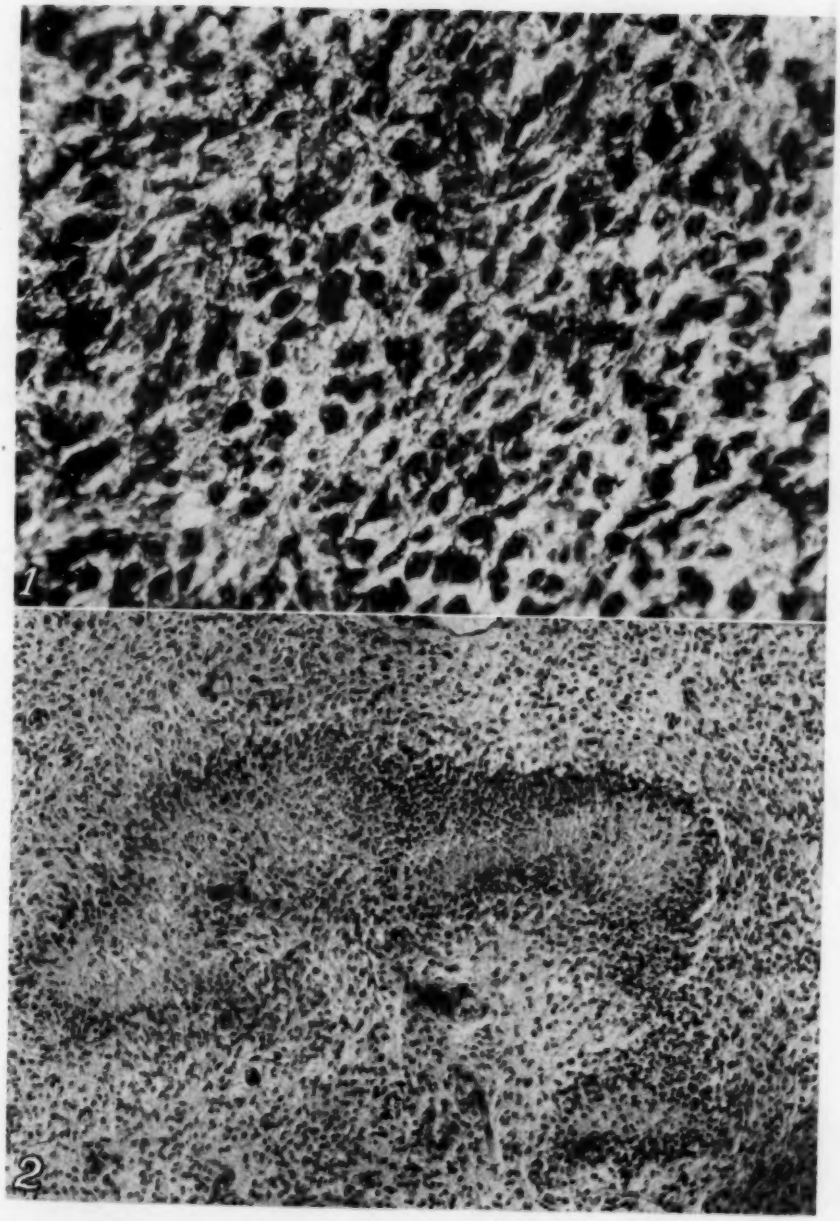
SPONGIOBLASTOMA MULTIFORME

Fig. 1 (P. B. B. H., Path. no. N-26-134).—Although the prevailing cellular type is spindle-shaped, there is a tendency to form astrocytes. Delicate neuroglial fibrils are produced which may be differentially stained, but the true shape of the cells is best seen in gold sublimate preparations in which the entire cytoplasm is impregnated. Cajal's gold sublimate method; × 300.

Fig. 2 (P. B. B. H., Path. no. A-16-82).—This tumor is always the seat of extensive degenerative processes, one of the most common of which is the formation of "palisades," as shown in this illustration. Hematoxylin and eosin; × 100. (For other details see Bailey and Cushing, footnote 2, pp. 73-81.)

(Many subgroups have been distinguished, such as tumors consisting of spindle cells, round cells, giant cells, ameboid cells and other types of cells, but there is no practical advantage in doing so, as the behavior of all these subgroups is identical.)

PLATE IX



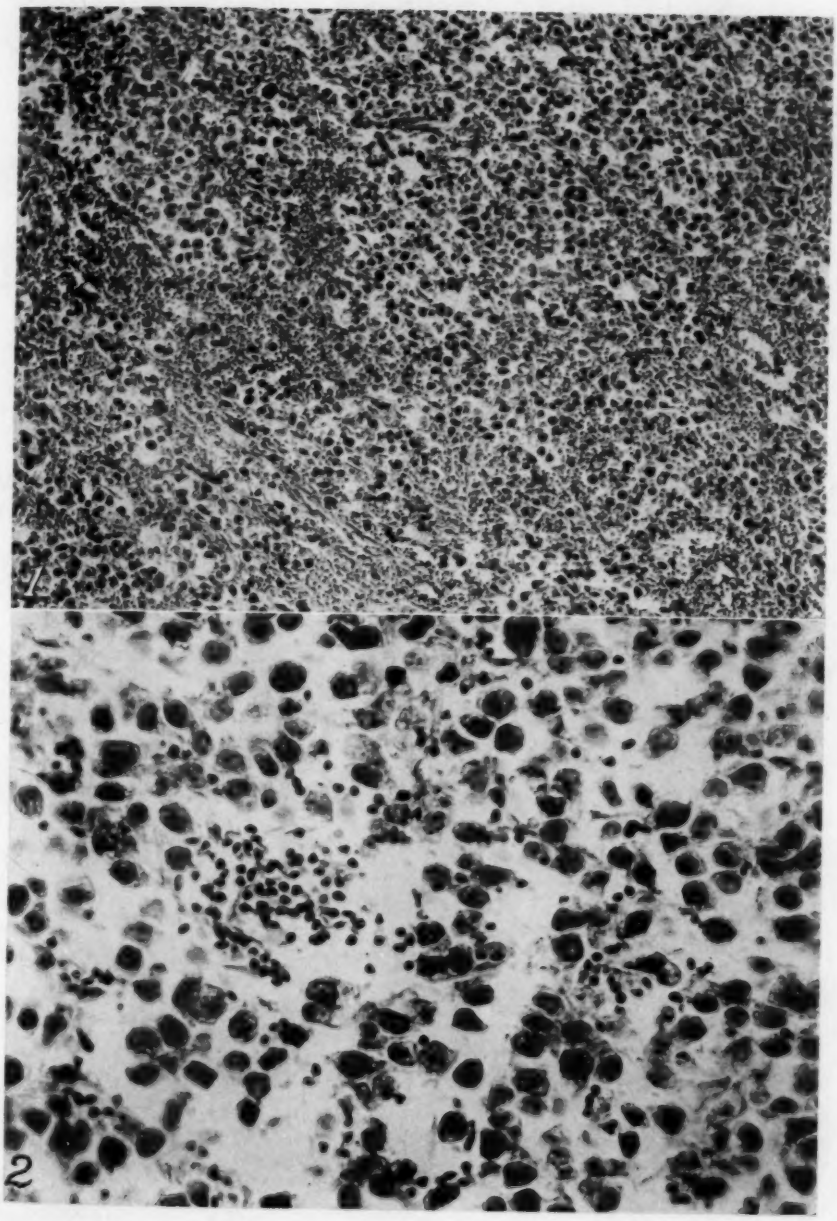
Explanation of Plate X

PINEALOMA

Fig. 1 (P. B. B. H., Path. no. NA-21-32).—Under low magnification, the pinealoma presents a characteristic appearance, consisting of an admixture of two tissues, one composed of large epithelioid cells with vesicular nuclei, and the other of lymphoid cells. Tumors with this structure arise only from the pineal body. They are sometimes known as chorioma or compound pineal gland type. Hematoxylin and eosin; × 100.

Fig. 2 (P. B. B. H., Path. no. NA-21-32).—The same two tissues are shown here at a higher magnification. Typical neuroglial cells are also found occasionally, but they are not shown in this illustration. (For further details see Horrax and Bailey, Arch. Neurol. & Psychiat. **13**:423 [April] 1925). Hematoxylin and eosin; × 300.

PLATE X



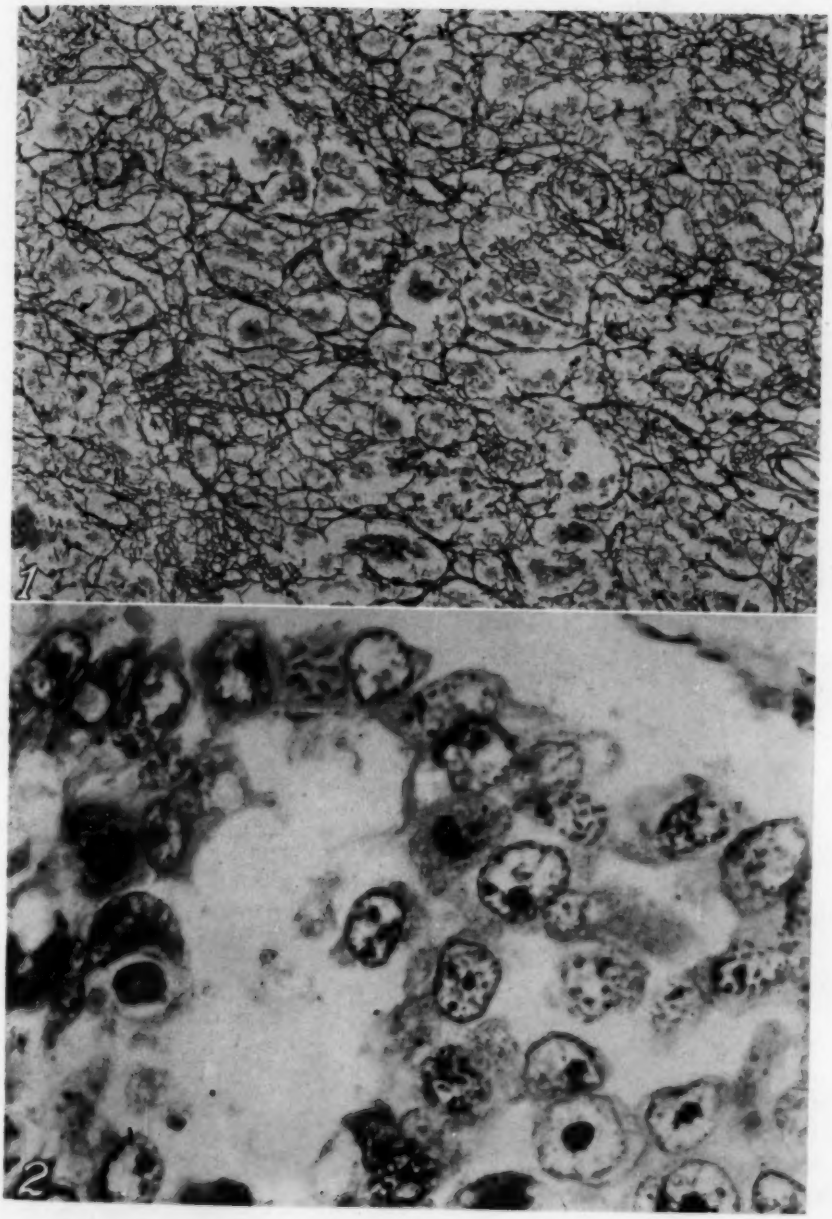
Explanation of Plate XI

PINEALOMA

Fig. 1 (P. B. B. H., Path. no. NA-22-16).—The lymphoid cells are contained within an abundant meshwork of reticulin, as is clearly shown here. Perdrau's ammoniacal silver method; × 80.

Fig. 2 (P. B. B. H., Path. no. NA-25-28).—The large epithelioid cells correspond to the cells of the pineal parenchyma. They sometimes have short processes ending in bulbs and often groups of granules and short rods known as blepharoplasten may be seen in their cytoplasm. A typical group is shown in the upper part of this figure. The nuclei of these cells are large and vesicular with prominent nucleoli. Neutral ethyl violet-orange G; × 850.

PLATE XI



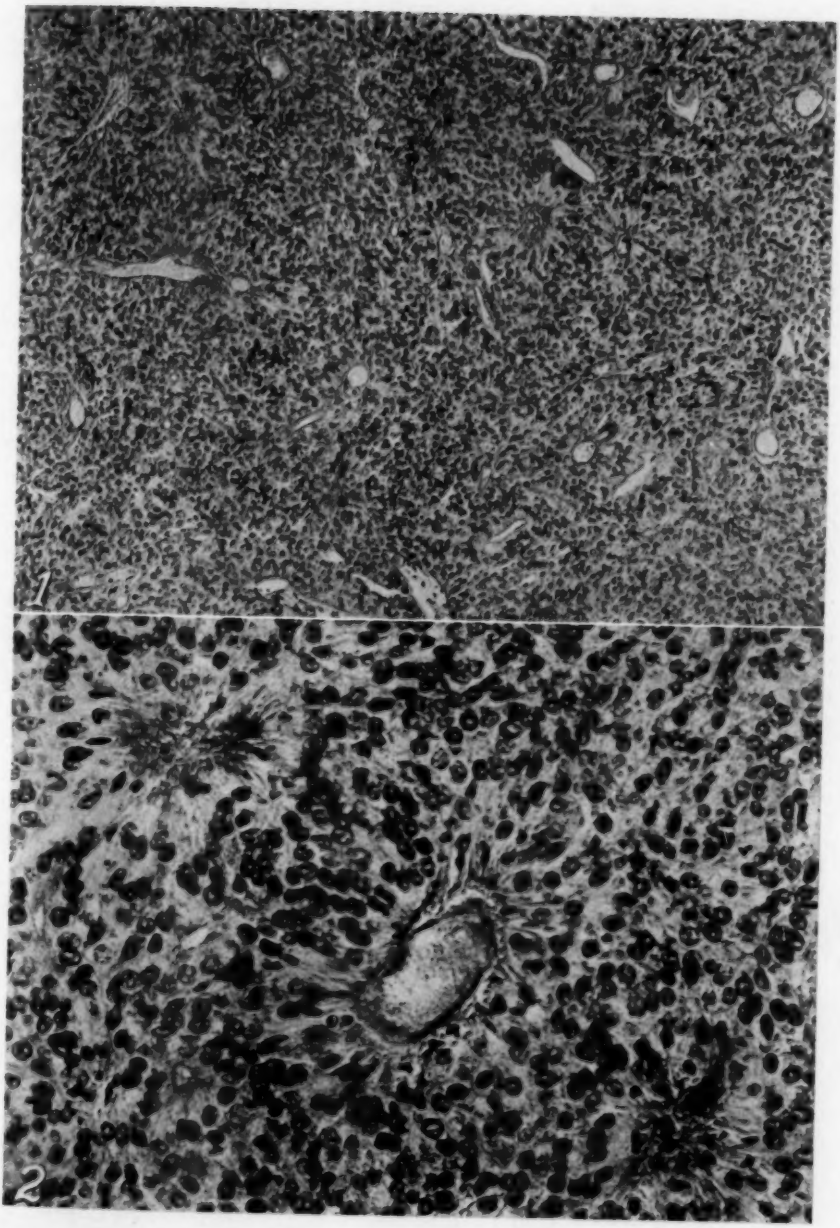
Explanation of Plate XII

EPENDYMOMA

Fig. 1 (P. B. B. H., Path. no. N-26-71).—These tumors are cellular but grow slowly. The cells near the vessels often radiate around them to form pseudorosettes. True rosettes may be found rarely, as in neuro-epitheliomas, two of which are shown in the upper part of this illustration. Hematoxylin and eosin; × 100.

Fig. 2 (P. B. B. H., Path. no. N-26-71).—Pseudorosettes are seen here. The extensions of the cells which are attached to the vessels stain feebly with methods for neuroglial fibrils. These tumors are usually described as ependymal gliomas. Hematoxylin and eosin; × 300.

PLATE XII



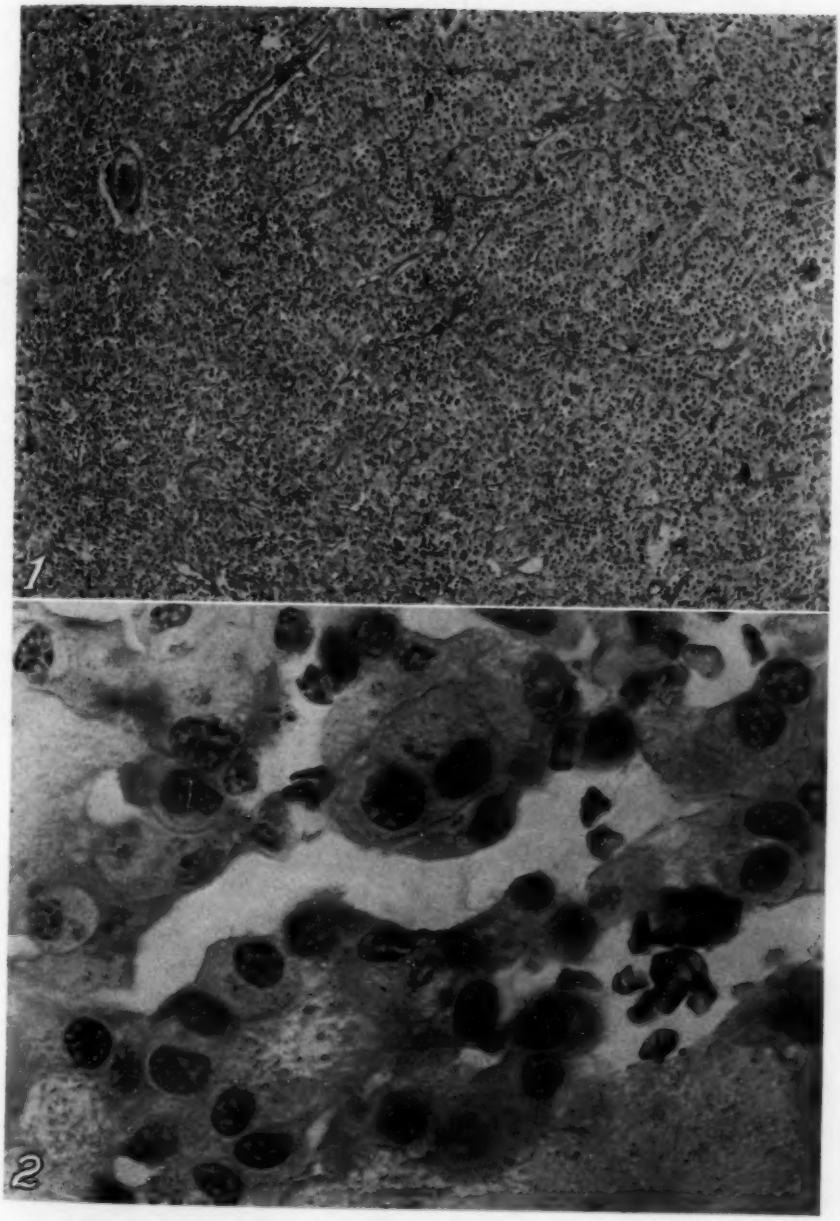
Explanation of Plate XIII

EPENDYMOMA

Fig. 1 (P. B. B. H., Path. no. S-14-433).—In some of the ependymomas, the cells are almost exclusively polygonal with abundant coarsely granular cytoplasm and well-defined cellular boundaries, as in this illustration. In others, one extremity is elongated so that the cells assume the shape of ependymal spongioblasts; part of the ependymomas under the term of ependymoblastomas may be distinguished on this basis, but there does not seem to be any practical advantage in doing so. Neutral ethyl violet-orange G; × 80.

Fig. 2 (P. B. B. H., Path. no. N-22-51).—In the cytoplasm of the cells of the ependymomas lie groups of granules or short rods that stain sharply with methods for neuroglial fibrils. They are known as blepharoplasten and may be clearly seen in this figure. Neutral ethyl violet-orange G; × 850. (For further examples, see Bailey, Arch. Neurol. & Psychiat. **11**:1 [Jan.] 1924, and Ann. d'Anat. path. Méd.-Chir. **2**:481. 1925.)

PLATE XIII



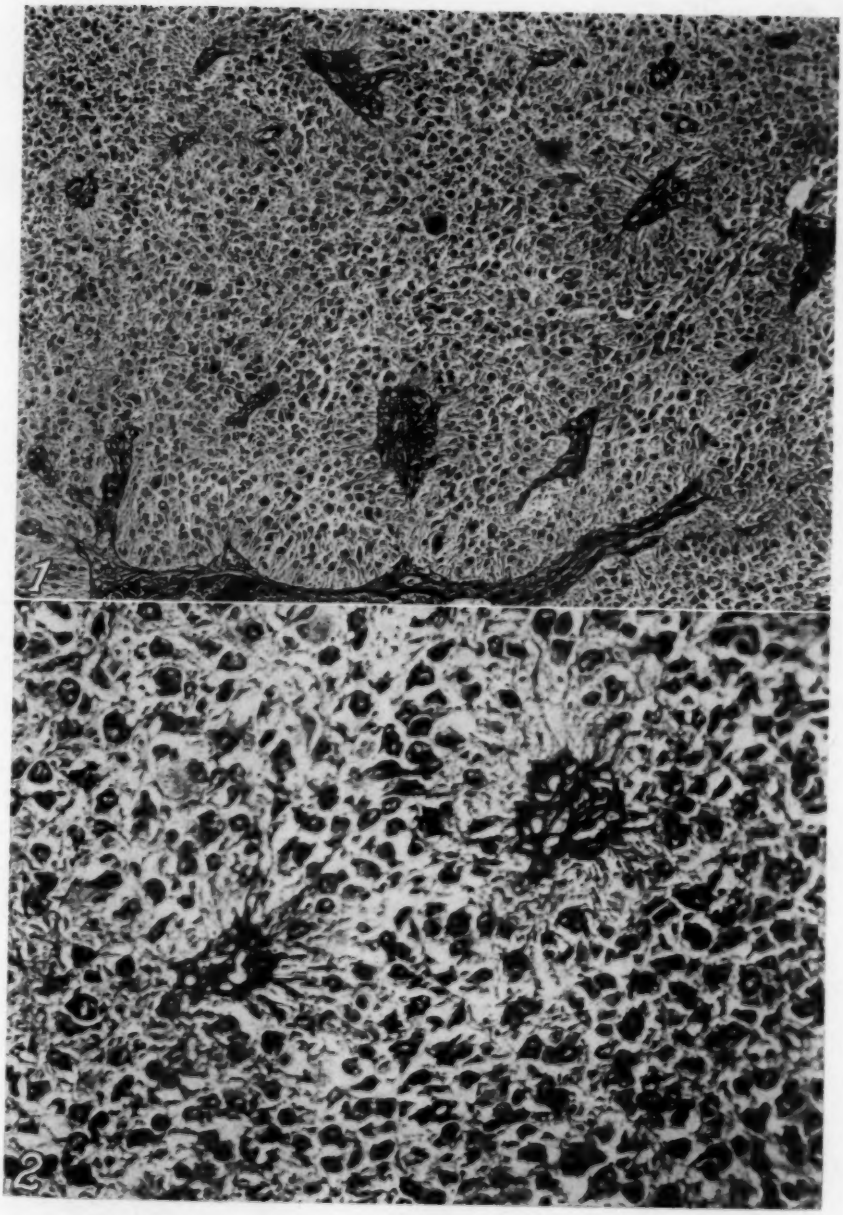
Explanation of Plate XIV

ASTROBLASTOMA

Fig. 1 (P. B. B. H., Path. no. N-23-76).—This photomicrograph shows well the loose texture of these tumors and the hypertrophy of the vascular walls which is common. Hematoxylin and eosin; × 100.

Fig. 2 (P. B. B. H., Path. no. N-23-76).—The radiation of the cells around the vessels is not clearly shown by this stain. The angular cell body with an apical process has caused these tumors to be described as ganglion cell gliomas. That the neoplastic cells are astroblasts and not neuroblasts is evident from plate XV. Hematoxylin and eosin; × 300.

PLATE XIV



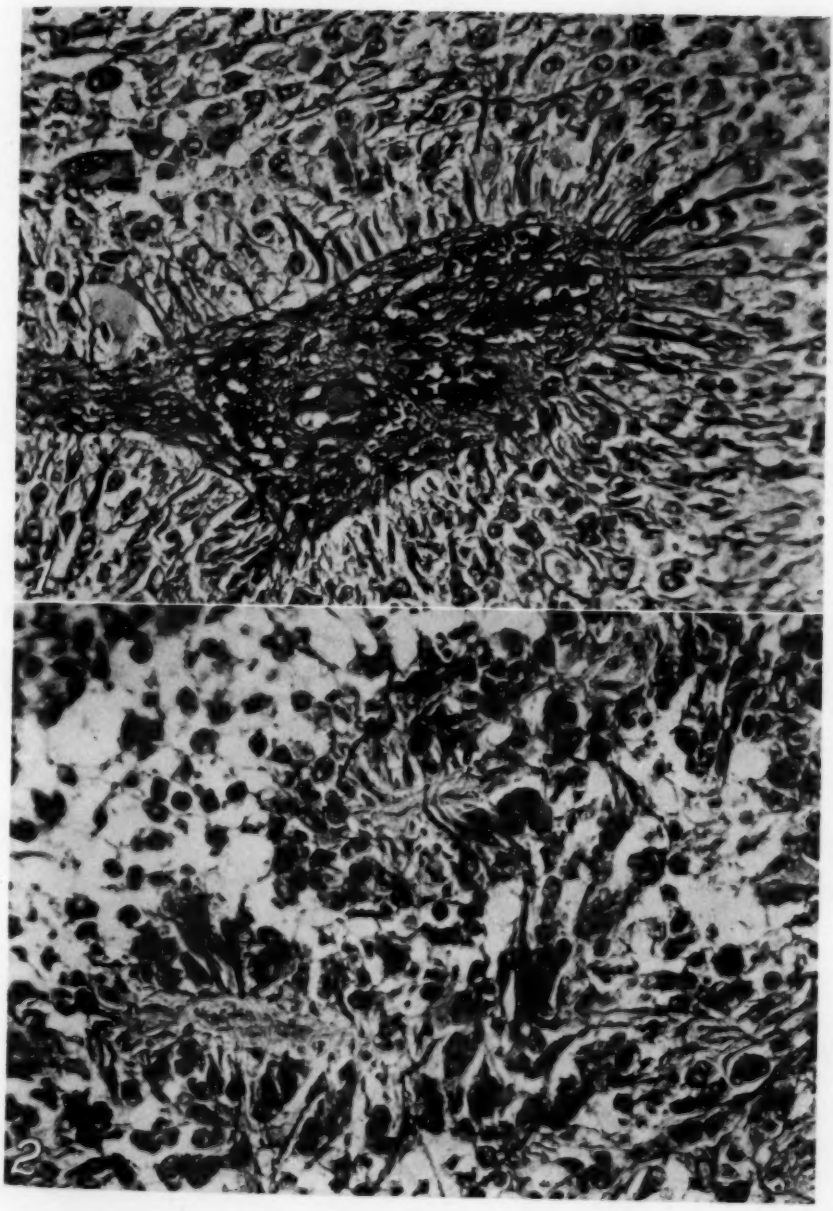
Explanation of Plate XV

ASTROBLASTOMA

Fig. 1 (P. B. B. H., Path. no. N-23-76).—The perivascular "feet" of the astroblasts are portrayed clearly. There are also feeble processes from the other extremity of the cell body. Groups of blepharoplasten are not found as in the ependymomas, to which there may be a superficial resemblance due to radiation of the cells around the blood vessels. There is also a greater variation in the size and shape of the cells and of their nuclei. Giant cells are often seen. Phosphotungstic acid hematoxylin; × 300.

Fig. 2 (P. B. B. H., Path. no. N-26-67).—These tumors have a great tendency to degenerate between the vessels, leaving only those cells which have perivascular "feet," as in this illustration. Phosphotungstic acid hematoxylin; × 300. (Reproduced by permission of the Williams and Wilkins Company).

PLATE XV



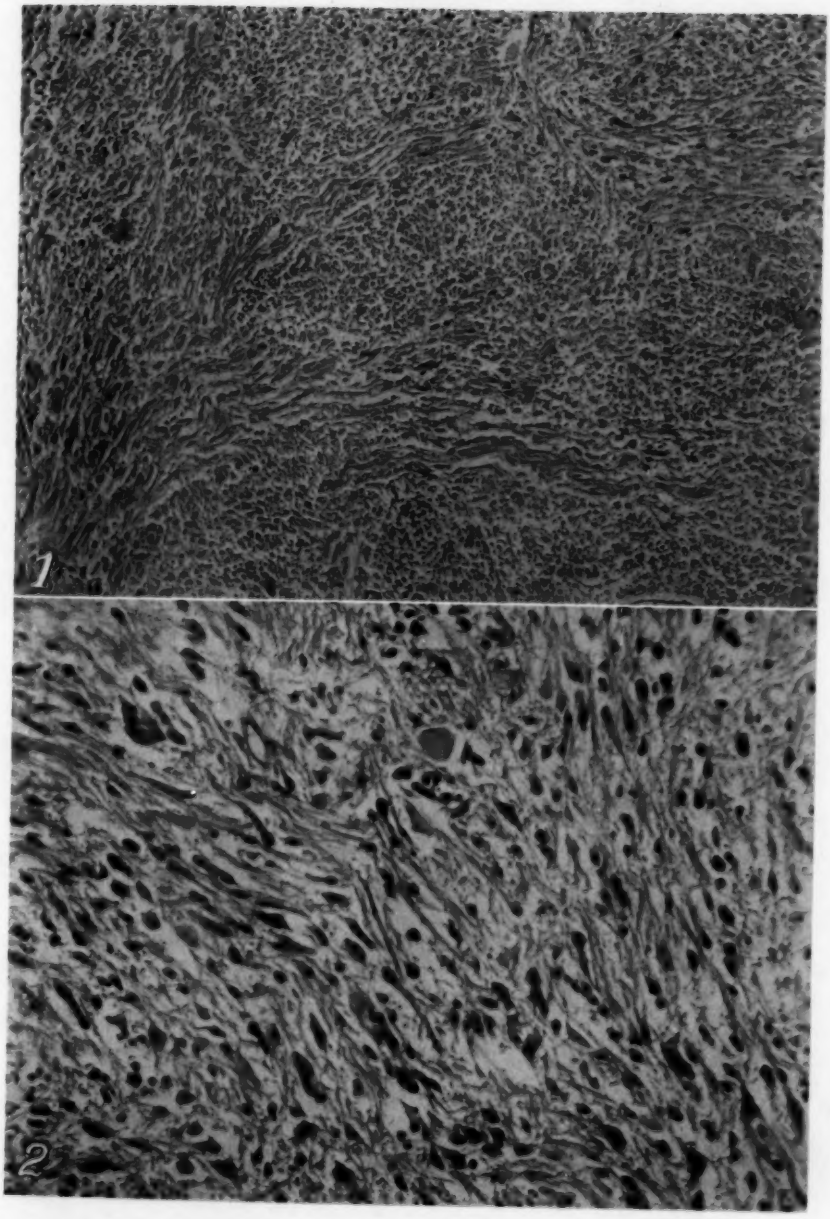
Explanation of Plate XVI

SPONGIOBLASTOMA UNIPOLARE

Fig. 1 (P. B. B. H., Path. no. A-19-54).—These tumors often present a striking resemblance microscopically to acoustic neurinomas, hence the name neurinoma centrale sometimes applied to them. In the present instance the cells are separated by edema, thus displaying their structure to better advantage. They are indolent tumors in which mitoses are rarely found. Hematoxylin and eosin; × 100.

Fig. 2 (P. B. B. H., Path. no. A-19-54).—At a higher magnification, the difference between these tumors and the acoustic neurinomas is more clearly seen. They lack the delicate reticular fibrils of the latter growths, and are composed for the most part of tadpole-shaped cells, the tails of which are round and hard like wires; they stain heavily with eosin and feebly with methods for neuroglial fibrils. Many bipolar spongioblasts are also present; rarely, astrocytes. Hematoxylin and eosin; × 300.

PLATE XVI



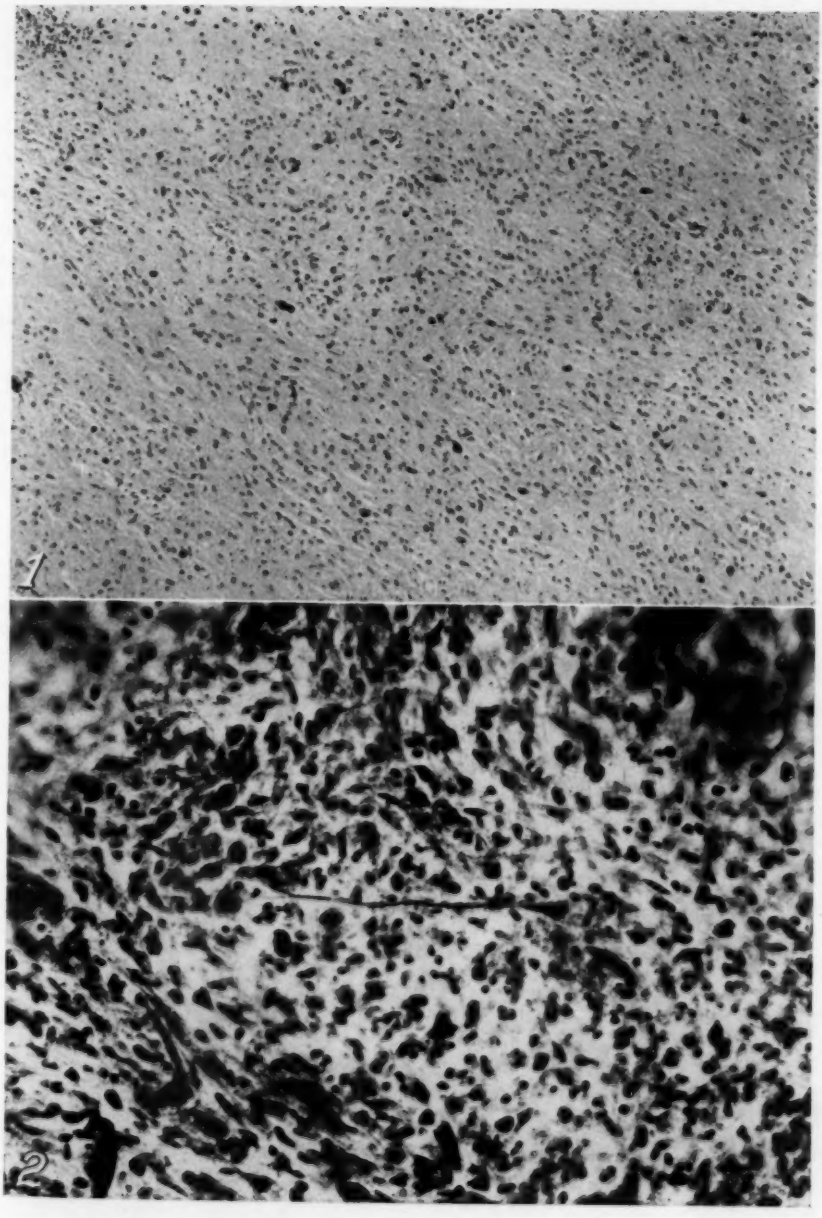
Explanation of Plate XVII

SPONGIOBLASTOMA UNIPOLARE

Fig. 1 (P. B. B. H., Path. no. N-20-20).—The structure of these tumors is often more compact than that of the one photographed in plate XVI. Another variant is sometimes produced by intervascular degeneration, so that the cells form clumps around the vessels. Hematoxylin and eosin; × 100.

Fig. 2 (P. B. B. H., Path. no. A-19-54).—Most of the cells in this photomicrograph have been sectioned transversely, but one, by a lucky chance, lies in the plane of section and shows well the silhouette of a typical unipolar spongioblast. Achúcarro's tannic silver method; × 300. (Reproduced by courtesy of the J. B. Lippincott Company.)

PLATE XVII



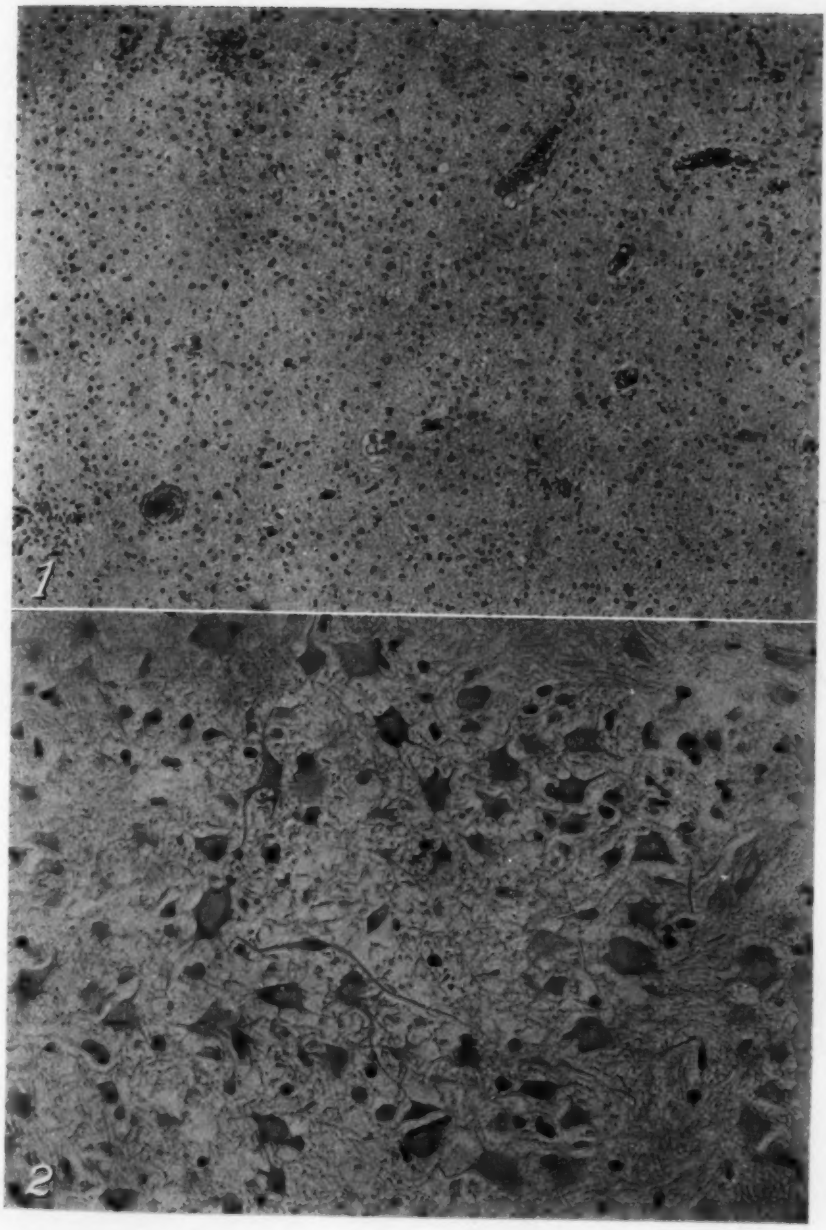
Explanation of Plate XVIII

ASTROCYTOMA

Fig. 1 (P. B. B. H., Path. no. N-26-166).—This illustration shows well the appearance of an astrocytoma at low magnification, with its nuclei scattered widely and evenly over the field. Hematoxylin and eosin; × 100.

Fig. 2 (P. B. B. H., Path. no. N-26-166).—The neoplastic cells are mostly astrocytes with numerous long processes forming an intricate meshwork. One bipolar spongioblast is also shown here. The nuclei are often eccentric, owing to the hyaline degeneration which is frequently present in the bodies of the cells of these tumors. Hematoxylin and eosin; × 300.

PLATE XVIII



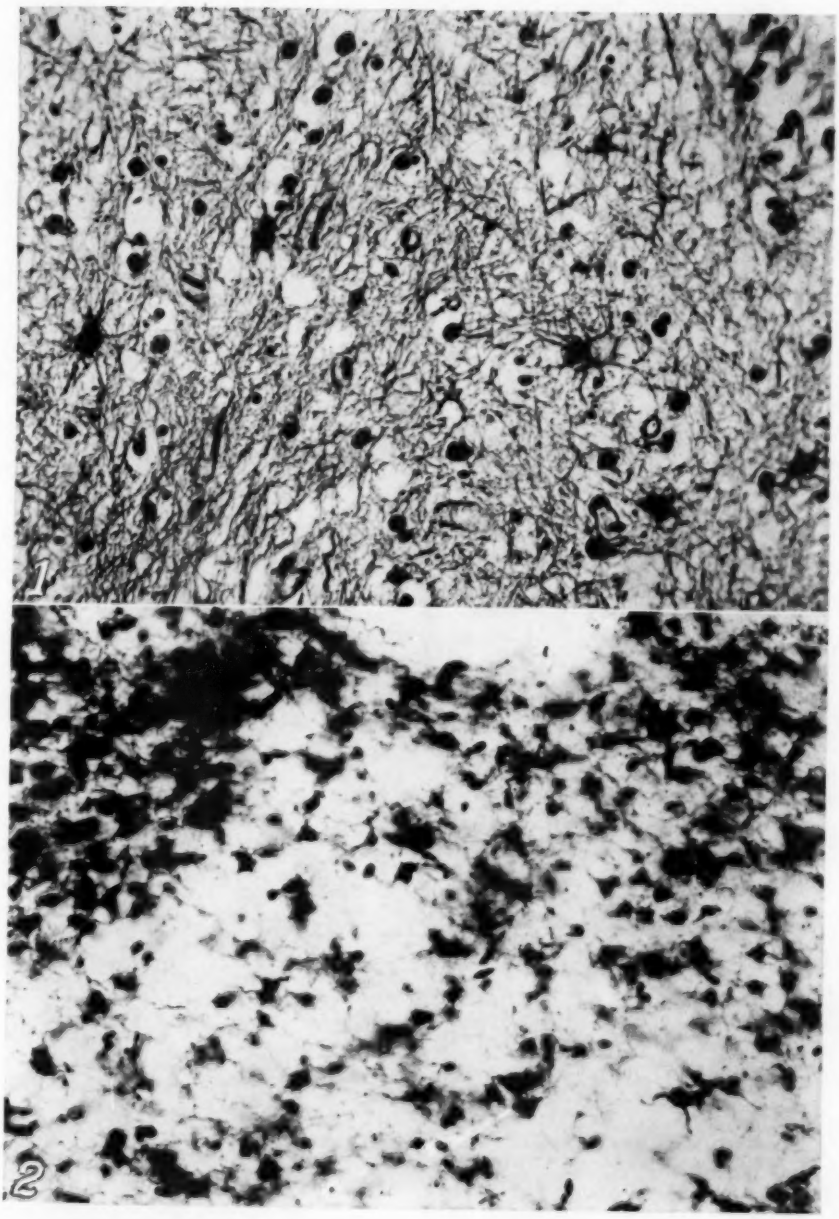
Explanation of Plate XIX

ASTROCYTOMA

Fig. 1 (P. B. B. H., Path. no. NA-25-22).—The shape of the neoplastic cells is better demonstrated by this staining method than by hematoxylin and eosin. Numerous neuroglial fibrils are usually formed. This illustration is taken from a fibrillary astrocytoma. Phosphotungstic acid hematoxylin; × 300.

Fig. 2 (P. B. B. H., Path. no. N-24-115).—In some of these tumors, neuroglial fibrils are not formed, the cells being exclusively protoplasmic astrocytes. Their structure can then be demonstrated only by some method for impregnating their cytoplasm. This photomicrograph also shows the tendency to cystic degeneration so common in these growths. Cajal's gold sublimate method; × 300.

PLATE XIX



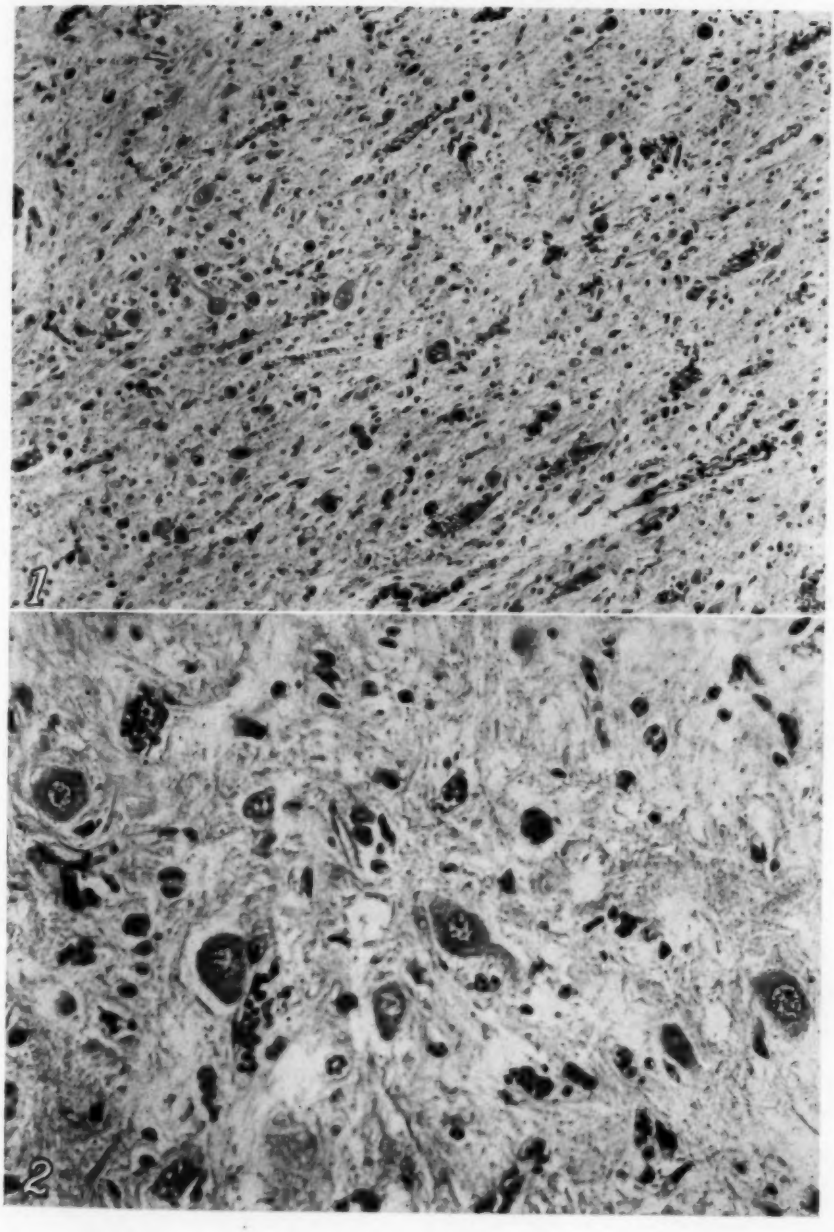
Explanation of Plate XX

GANGLIONEUROMA

Fig. 1 (P. B. B. H., Path. no. NA-25-36).—Ganglion cells and calcospherites are seen. Hematoxylin and eosin; × 100.

Fig. 2 (P. B. B. H., Path. no. NA-25-36).—Ganglion cells are shown at a higher magnification. The intervening tissue is composed of cells analogous to spongioblasts or to the neurilemmal and capsular cells of the peripheral nerves and ganglions. Hematoxylin and eosin; × 300.

PLATE XX



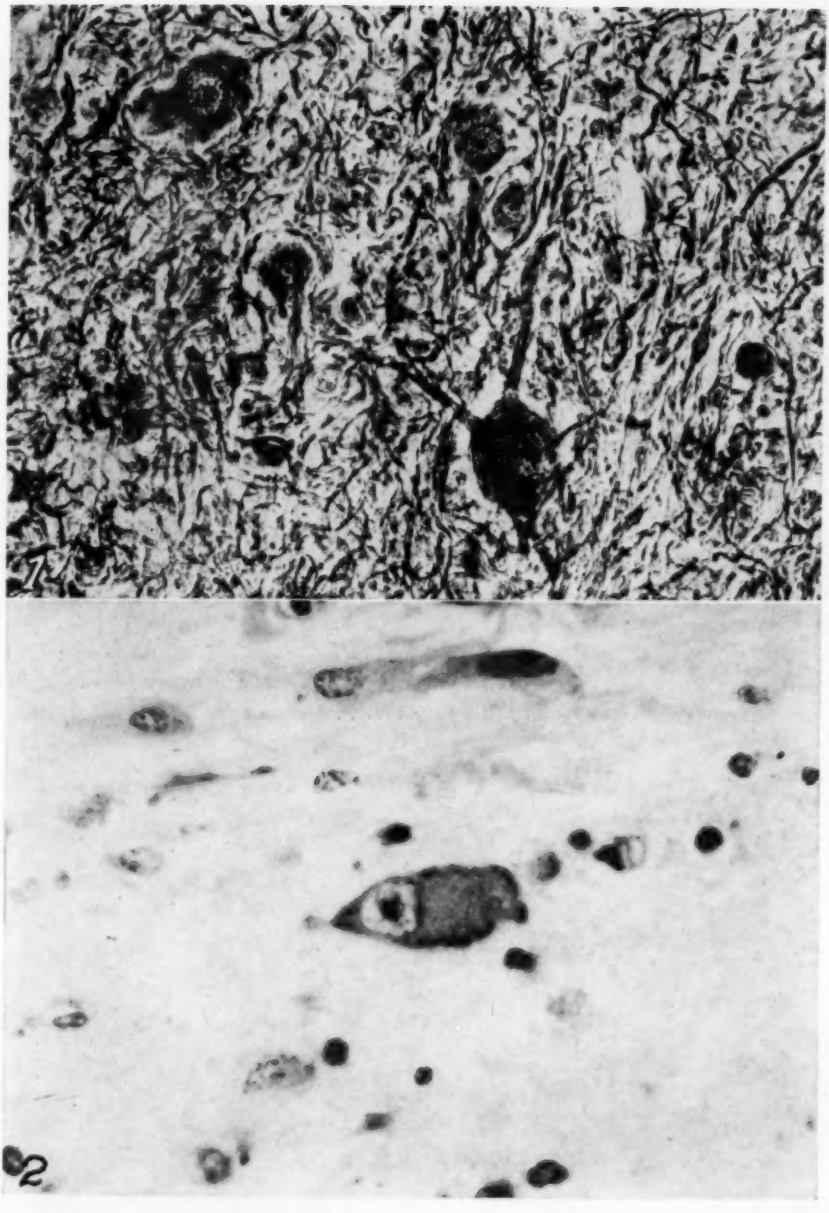
Explanation of Plate XXI

GANGLIONEUROMA

Fig. 1 (P. B. B. H., Path. no. NA-25-36).—Neurofibrils are shown in the processes of the ganglion cells. Numerous unmyelinated nerve fibers form a meshwork. Cajal's reduced silver method; × 450.

Fig. 2 (P. B. B. H., Path. no. NA-26-23).—Tigroid bodies are being formed in the periphery of the cytoplasm of a neoplastic ganglion cell. Cresyl violet method of Bielschowsky-Plein; × 850.

PLATE XXI



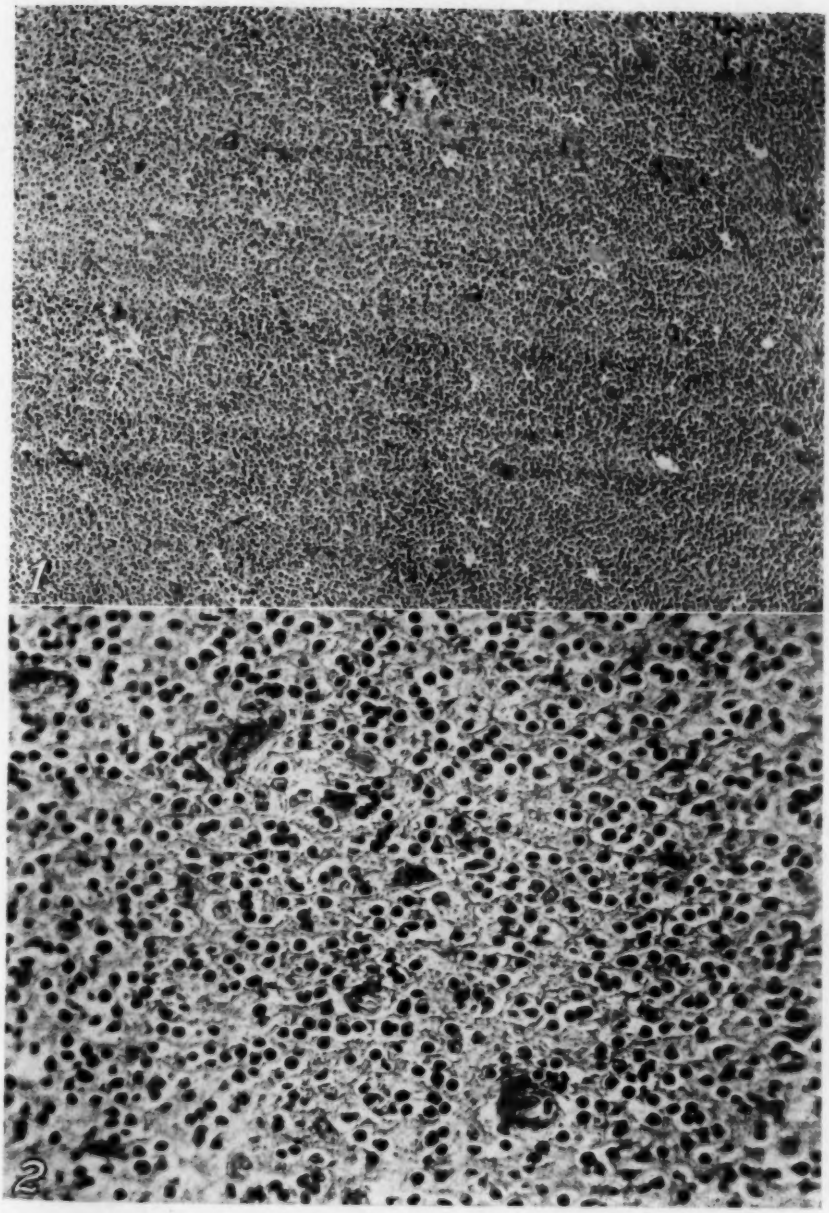
Explanation of Plate XXII

OLIGODENDROGLIOMA

Fig. 1 (P. B. B. H., Path. no. S-16-925).—This tumor, although very cellular, rarely contains mitotic figures and is often calcified. Hematoxylin and eosin; × 100.

Fig. 2 (P. B. B. H., Path. no. S-16-925).—The nuclei of the neoplastic cells are mainly small and spherical, with a heavy chromatinic network like those of the oligodendroglia. Hematoxylin and eosin; × 300.

PLATE XXII



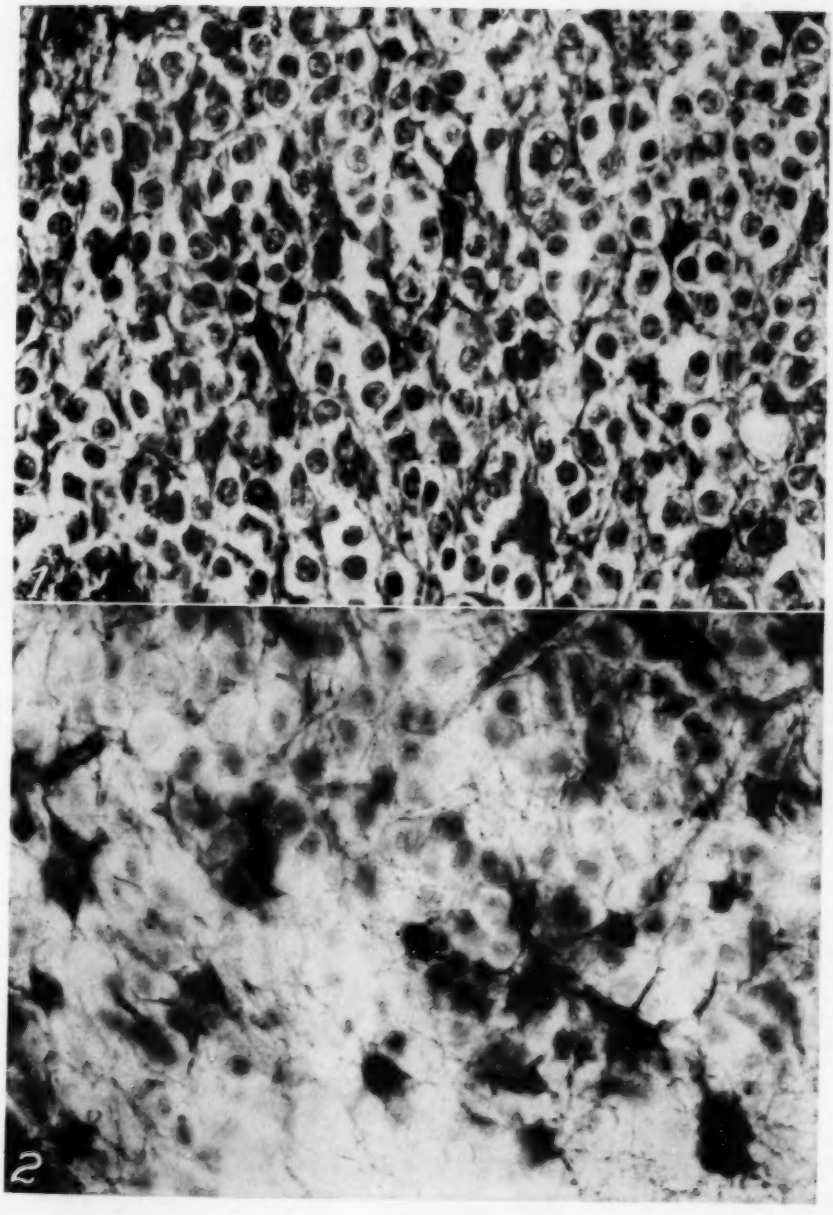
Explanation of Plate XXIII

OLIGODENDROGLIOMA

Fig. 1 (P. B. B. H., Path. no. S-16-925).—Scattered among the smaller cells, protoplasmic astrocytes are found the processes of which form most of the scanty intercellular fibrillary material. Mallory's aniline blue-orange G; × 600.

Fig. 2 (P. B. B. H., Path. no. N-24-71).—The small protoplasmic astrocytes are clearly demonstrated by this method, but are difficult to photograph in the thick frozen sections. Cajal's gold sublimate method; × 600.

PLATE XXIII



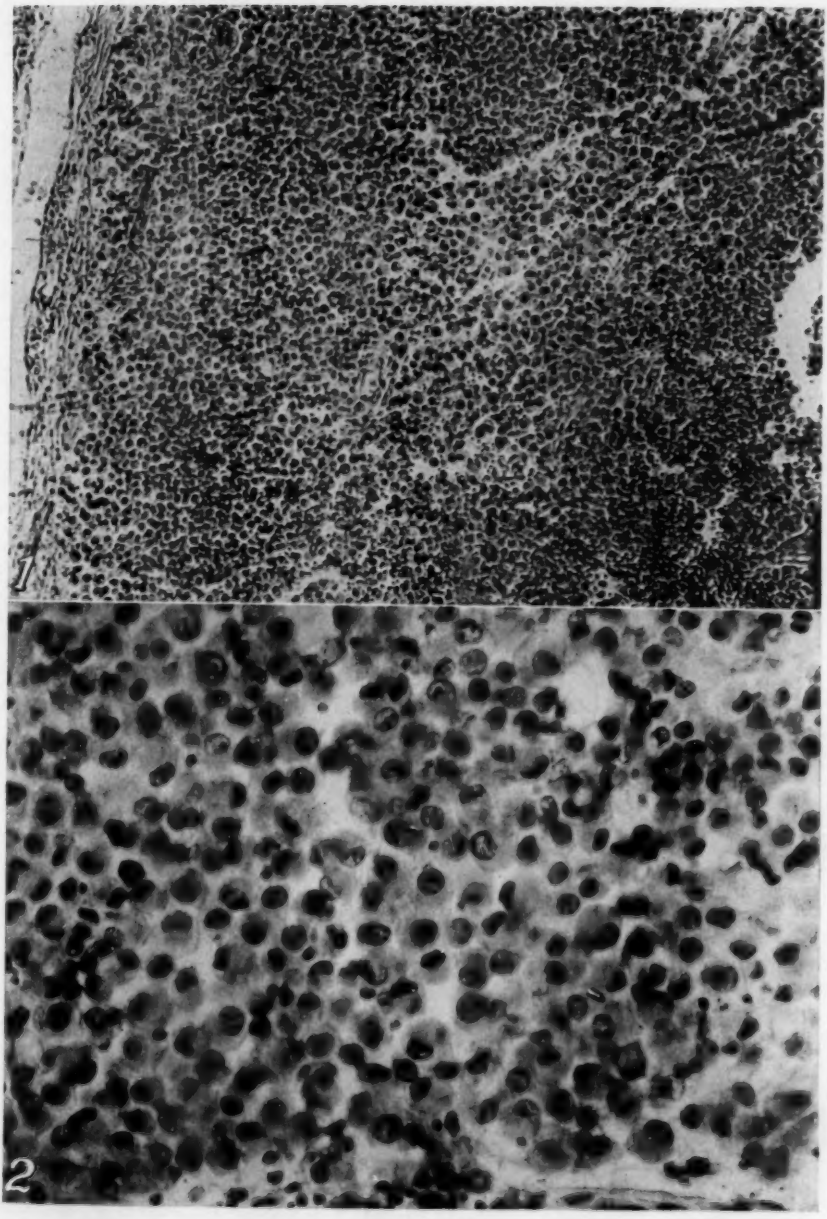
Explanation of Plate XXIV

NEUROBLASTOMA APOLARE (?)

Fig. 1 (J. H. H., Surg. no. 22551).—A rare tumor occurs in the cerebral hemispheres which is composed of large round cells with large vesicular nuclei. Such a tumor of the gasserian ganglion was described by Marchand. The cells are probably apolar neuroblasts, although we have never been able to secure material properly fixed for specific impregnation methods. Hematoxylin and eosin; × 100.

Fig. 2 (J. H. H., Surg. no. 22551).—The cells resemble somewhat those of the pineal parenchyma found in the pinealomas, but do not contain blepharoplasten. Hematoxylin and eosin; × 300.

PLATE XXIV



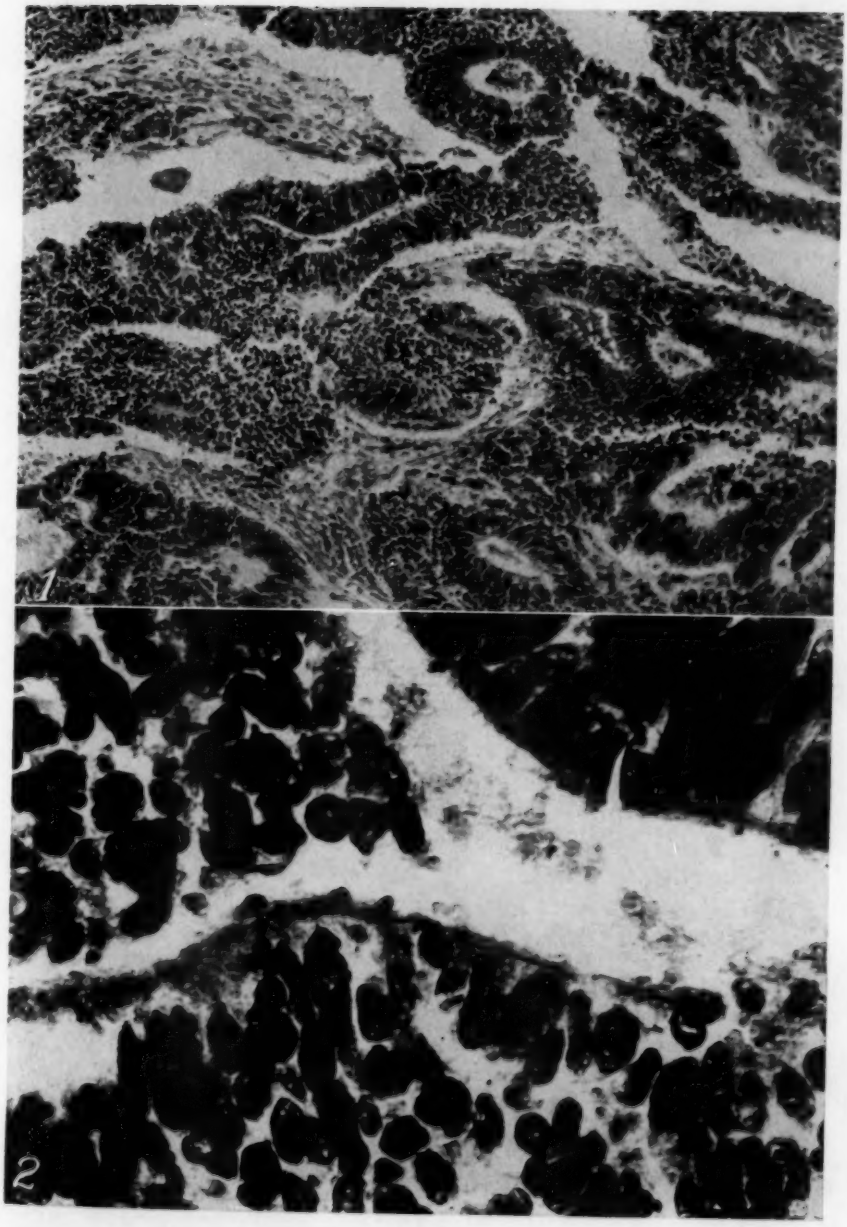
EXPLANATION OF PLATE XXV

MEDULLO-EPITHELIOMA (?)

Fig. 1 (P. B. B. H., Path. no. NA-22-16).—Often in teratomas and occasionally in simple gliomas the neoplastic cells, which are very embryonic and divide rapidly, have a tendency to form medullary tubes. Methylene blue and eosin; × 100. (See Klapproth: Centralbl. f. allg. Pathol. u. path. Anat. **32**:617, 1922, plate fig. 2.)

Fig. 2 (P. B. B. H., Path. no. NA-22-16).—The cells surrounding these tubes resemble the rosette cells of the neuro-epitheliomas, but differ from them in not having blepharoplasten. Instead, there is a tendency to form an internal limiting membrane like that of the retina. Phosphotungstic acid hematoxylin; × 850.

PLATE XXV



THE HEART IN SYPHILITIC AORTITIS*

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Four important points are to be considered in studying syphilitic aortitis: the aneurysm, the narrowing of the orifices of the coronary arteries, aortic insufficiency and the condition of the myocardium.

The purpose of this study of 126 hearts associated with syphilitic aortitis is to observe the anatomic changes in the valves, coronary arteries, myocardium and pericardium, and to note the immediate relation of these changes to the cause of death.

There were 126 cases of syphilitic aortitis in the necropsy material at the University of Minnesota from 1910 to 1926. During this period 4,577 necropsies were performed on the bodies of persons over 20 years of age who died from other causes. This gives an incidence of 2.6 per cent.

The death rate from syphilitic aortitis is greatest in the fifth and sixth decades. As a comparison, it is interesting to observe the decades in which most deaths occur in other forms of cardiac failure: acute rheumatic, second decade; recurrent rheumatic, fourth decade; bacterial endocarditis, third decade; old valvular defects, fifth decade; hypertensive cardiac failure and coronary sclerosis, sixth decade.

The men in this series of 126 cases outnumber the women in the proportion of 104 to 22. This preponderance is not so great as it appears, however, when it is considered that the ratio of men to women in the necropsy material is 2.5 to 1. With this correction, the ratio is about 2 men to 1 woman.

The 126 cases of syphilitic aortitis are classified on the basis of their clinical courses and the pathologic conditions at necropsy as follows:

1. Aortic insufficiency: forty-six cases, 36.5 per cent.
2. Sudden death from closure of coronary orifices: twenty-five cases, 19.9 per cent.
3. Rupture of aortic aneurysm: thirty-five cases, 27.7 per cent.
4. Gummas of the myocardium: three cases, 2.4 per cent.
5. Miscellaneous (death from other causes): seventeen cases, 13.5 per cent.

AORTIC INSUFFICIENCY

The cases in the group showing aortic insufficiency ran a clinical course of cardiac decompensation. The duration varied from a few

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days to six years. Forty-six of the 126 hearts fall into this group, though narrowing of the orifices of the coronary arteries was in many cases a contributory cause of death. Twenty-eight of these forty-six hearts are preserved for study. The anatomic description is confined to these hearts (table 1).

In comparing syphilitic involvement of the aortic cusps with aortic valvular defects of rheumatic origin, the following facts were noted: In a series of ninety-eight old valve defects of rheumatic origin, aortic

TABLE 1.—*Aortic Insufficiency*

Age	Sex	Marginal Thickening	Separation of Cusps	Left Coronary Orifice	Right Coronary Orifice	Distal Left Coronary	Distal Right Coronary	Weight of Heart	Gross Myocardial Fibrosis	Microscopic Myocardial Fibrosis	Reaction in Myocardium	Pericarditis: Old	Pericarditis: Acute	Pericarditis: Microscopic	Spirochetes
49	M	+	—	—	—	+	+	450	—	+	a	—	—	—	—
55	M	+	—	—	—	—	—	550	—	—	..	—	—	—	—
53	M	+	+	—	—	+	+	730	+	+	a	—	—	—	—
50	M	+	+	—	—	+	+	680	—	—	..	—	—	—	—
45	M	—	—	—	—	—	—	740	—	+	a	—	—	—	—
50	M	+	+	—	—	—	—	700	—	—	..	—	—	—	—
32	M	+	+	—	½	+	—	685	—	—	..	—	—	—	—
58	M	+	—	½	—	—	—	725	—	+	p & L	+	—	L	—
41	F	+	+	1/10	—	—	—	475	—	—	..	—	—	—	—
24	M	+	+	½	½	—	—	800	—	+	a	—	—	—	—
48	M	+	+	½	—	—	—	500	—	—	..	—	—	—	—
35	M	—	+	½	—	—	—	475	—	+	p	—	—	—	—
35	M	+	+	½	O	—	—	500	—	+	a	—	—	—	—
38	F	+	—	¾	¼	—	—	560	—	—	..	—	—	—	—
44	M	+	+	¼	¼	++	+	760	—	+	p & a	—	—	—	—
52	M	—	—	½	¾	+++	+	600	—	++	a	—	—	—	—
51	M	+	+	½	O	—	—	775	—	—	..	—	—	—	—
61	M	+	+	½	O	—	—	650	—	—	..	—	—	—	—
44	M	+	+	½	½	—	—	520	—	—	..	—	—	—	—
50	M	—	—	¾	¾	+	+	500	—	—	..	—	—	—	—
45	M	+	+	¾	—	—	—	750	—	—	..	—	—	—	—
54	M	+	+	¾	O	+	+	700	—	—	..	—	—	pL	—
50	M	+	+	¼	¼	+	—	610	—	—	..	—	—	—	—
40	M	+	+	¼	¾	—	—	700	—	—	..	—	—	—	—
54	F	+	+	¼	—	—	—	400	—	—	..	—	—	—	—
53	M	+	+	½	—	+	+	510	—	—	..	—	—	—	—
35	M	+	+	¼	¼	—	—	660	—	+	a	—	—	—	—
47	M	+	+	½	½	—	—	675	—	+	a	+	—	—	—
		24	21												

In this and the following tables + indicates present; —, absent; a, atrophic; b, base at aortic ring; L, lymphocytes; p, proliferative; O, completely closed; *, many giant cells, and t, coronary thrombosis.

insufficiency was present fifty-one times (52 per cent); twenty times as pure insufficiency (20.4 per cent), eleven times as chiefly insufficiency and some stenosis (11.2 per cent), and twenty times as chiefly stenosis, but some insufficiency (20.4 per cent). In forty-six (36.5 per cent) of the 126 cases with syphilitic involvement of the aorta, death resulted from aortic insufficiency. In none of these was there an aortic stenosis or organic mitral injury. Aortic insufficiency without other valvular involvement was present in only thirteen of the ninety-eight cases (13.2 per cent). A pure aortic stenosis was present in seventeen of the ninety-eight cases, and in twelve of these seventeen it occurred without

the involvement of other valves. The fact that the aortic valve shows evidence of insufficiency is not a basis for a diagnosis of syphilitic aortitis or valvulitis.

Bollinger,[1] in 1902, described the shortening and insufficiency of the aortic cusps as the most frequent complication of syphilitic aortitis. He considered that the process in the valves was a continuation of the syphilitic lesion from the aorta. Gruber [2] stated that the valvular insufficiency was brought about by a fibrous, cordlike thickening and shrinking of the free margin of the valve. Lupu [3] also described a cordlike thickening on the free margin of the aortic cusps. In a study of twenty-five cases of syphilitic aortic insufficiency, Scott [4] found the architecture of the cusps distorted in every case.

Macroscopically, syphilitic valvulitis does not show any resemblance to acute rheumatic or bacterial endocarditis in which the lesion appears as vegetations on the ventricular surfaces of the aortic cusps about one third the distance from the free to the attached margin. In syphilitic valvulitis the involvement is confined to the free margin of the cusps almost entirely. No platelet thrombus is present, such as is always seen in bacterial endocarditis and frequently in acute rheumatic endocarditis. There can be no embolic processes, since there are no loose thrombi attached to the valves to form emboli. The lesion in the syphilitic valvulitis consists of a cordlike thickening of the free margins of the cusps (fig. 1). This thickening may be at the aortic attachments of the cusps alone, but generally it extends the full length of the free margin. As a rule, all the cusps are affected, but there may be one or two cusps or a part of a cusp involved. The cusp is not diffusely thickened, as in the rheumatic infection, and fusion of the cusps does not occur. The functional end-results of a syphilitic vulvulitis is similar to that of a defective valve resulting from a rheumatic infection, except that stenosis never occurs.

Herxheimer [5] states that in the early stage the thickened margin of the cusps is rich in cells, but that later it becomes hyalinized. Gruber [2] describes the cross-section of the cusp as having a clublike end which becomes hyalinized. From a microscopic study of several valves, Lupu [3] decided that the changes of the aortic cusps in syphilitic aortitis depend on a proliferative inflammatory process, which for the

1. Bollinger: Ueber Arteriosklerose, München. med. Wchnschr. **49**:641, 1902.
2. Gruber, G.: Ueber die Doehle-Heller'sche Aortitis, cited by Lupu, N.: Schweiz. med. Wchnschr. **50**:915, 1920.
3. Lupu, N.: Untersuchungen über die mikroskopischen Veränderungen der Aortenklappen bei Aortitis syphilitica, Schweiz. med. Wchnschr. **50**:915, 1920.
4. Scott, R. W.: Syphilitic Aortic Insufficiency, Arch. Int. Med. **34**:645 (Nov.) 1924.
5. Herxheimer, G.: Zur Atiologie und pathologischen Anatomie der Syphilis, Ergebn Path. u. Anat. **11**:186, 1907.

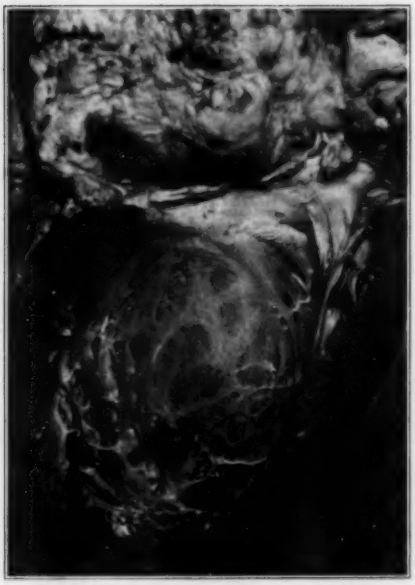

Fig. 1.—The aortic valve showing free marginal thickening and separation of the cusps at their attachment to the aorta.

Fig. 2.—Low power magnification of a cross-section of normal aortic cusp.

most part advances from the intima of the aorta through the marginal aortic attachments of the cusps. A thickened free margin is produced. He believes that the shortening or roughening of this margin is the chief cause of aortic insufficiency.

The normal valve, when studied in cross-section, shows the free margin tapering to a point (fig. 2). When the cross-sections of the cusps from syphilitic hearts are examined, various degrees of thickening are seen in the free margin (fig. 3). There is a proliferation of fibroblasts, as in the acute rheumatic valve (fig. 4). The proliferative change

Fig. 3.—Low power magnification of a cross-section of syphilitic aortic cusp showing marginal thickening.

extends from the aorta through the marginal aortic attachments of the cusps beneath the endocardial layer of both surfaces of the leaflet. These fibroblasts soon lay down collagenous fibers, and the entire thickened mass becomes a hyalinized scar. No reaction is detected in the sinus attachment of the cusps. A shrinking or wrinkling of this cord can and in many cases does shorten the free margin of the valve, and produces an insufficiency.

Another anatomic valvular injury of importance equal to that of the cordlike thickening of the free margins of the cusps is commonly

found. This injury consists of a proliferative growth of the intima of the aorta between the aortic attachments of the cusps so that the attachments are pushed apart (fig. 1). The cusps may be separated from one another as much as a centimeter, with evident insufficiency. Doehle [6] states that this type of lesion is not mentioned in textbooks of pathologic anatomy. He describes the condition as consisting of a proliferation with thickening of the intima of the aorta between the upper attachments of the aortic cusps to the aorta, so that the cusps are pushed apart, and a groove is formed between them.

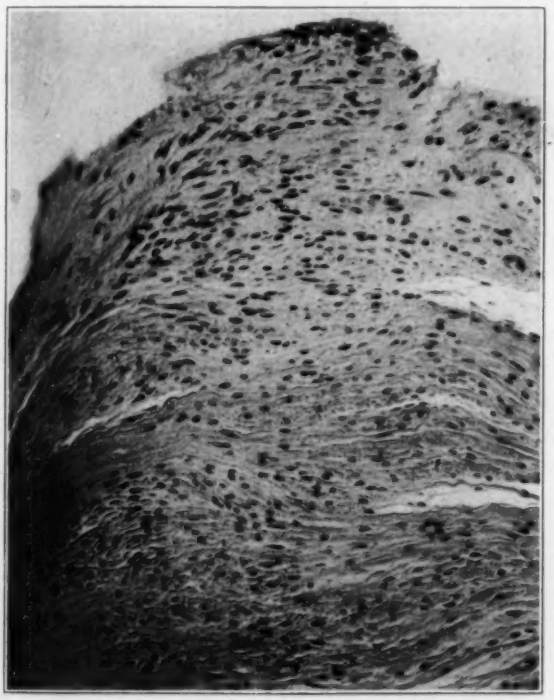

Fig. 4.—Section of the marginal thickened area of a syphilitic aortic cusp.

In our material this anatomic separation of the attachments was a frequent cause of insufficiency. A dilatation of the aortic orifice may be a third cause of insufficiency. This condition in itself appears to be of less frequent occurrence than either the free marginal thickening or the separation of the aortic attachments of the cusps.

In the twenty-eight hearts with aortic insufficiency, the free marginal cordlike thickening was present in twenty-four. The aortic attachments of the cusps were separated in twenty-one. One or both of these two

6. Doehle: Ueber das Charakteristiche der syphilitischen Erkrankung der Aortenklappen, Berl. klin. Wchnschr. **58**:1169, 1921.

anatomic changes were present in twenty-five of the twenty-eight cases. In the twenty-five there was evident gross anatomic cause for the decompensation. In the remaining three cases with clinical and pathologic evidence of cardiac decompensation, dilatation of the aortic ring may have accounted for the insufficiency and failure.

Warthin,[7] in a study of twelve cases of congenital cardiac syphilis, came to the conclusion that syphilis of the heart may lead to coronary sclerosis. In a study of another series of eight cases of sudden death due to syphilis of the heart, he[8] mentions syphilitic disease of the coronary arteries with resulting infarction and fibrosis as a cause of death. Brooks[9] reported coronary injury in thirty-five of fifty cases of syphilitic aortitis. Little is said in the literature with regard to the localization and character of the involvement of the coronary arteries in cases of syphilitic aortitis.

Except in the orifices, the coronary arteries in these twenty-eight hearts showed little gross change. In twenty-two of the twenty-eight, narrowing was noted in one or both of the orifices. None of the left coronary orifices were completely closed, but they were reduced in diameter, being from three-quarters to one-tenth of the normal. In four cases, the right coronary orifices were completely closed. In the remaining eleven the diameters ranged from three-quarters to one-eighth of the normal. The reaction about the coronary orifices was syphilitic. Although these twenty-eight were primarily cases of valvular insufficiency, it is apparent that the narrowing of the coronary orifices is a common anatomic contributing cause of the cardiac failure.

In only nine of the twenty-eight hearts was there any gross pathologic change in the coronary arteries distal to the orifices. These nine cases showed a thickening of the walls with atheromatous intimal changes, namely, the ordinary senile type of coronary arterial disease. In seven of the hearts this senile sclerosis was only slight, and in the two others it was of moderate severity. Nothing was seen in microscopic sections of these arteries that was different form ordinary senile arteriosclerosis. A sclerosis of this kind and degree is not infrequent in persons over 45 years of age, and apparently it was not a factor of importance in producing heart failure in these twenty-eight cases.

The most conspicuous anatomic change noted in the myocardium with aortic insufficiency is cardiac hypertrophy. This is in accord with Scott's[4] report in which he noted left ventricular hypertrophy similar to that in hypertensive hearts in all of his twenty-five cases. The hyper-

7. Warthin, A. S.: Congenital Syphilis of the Heart, Am. J. M. Sc. **141**:398, 1911.

8. Warthin, A. S.: Syphilitic Myocarditis, Am. Heart J. **1**:1, 1924.

9. Brooks, H.: The Heart in Syphilis, Am. J. M. Sc. **146**:513, 1913.

trophy is confined chiefly to the left ventricle, but frequently some enlargement is noted in the right ventricle. The average increase in weight of the heart is fully as great as that found in cardiac failure with essential hypertension. This hypertrophy appears to be the result of the aortic insufficiency.

The largest heart of a man in this group of aortic insufficiency weighed 950 Gm.; the smallest, 355 Gm., and the average weight was 620 Gm. The largest heart of a woman weighed 630 Gm.; the smallest, 400 Gm., and the average was 483 Gm. The hypertrophy in twenty-five of the twenty-eight cases could be accounted for by the anatomic valvular changes. In the remaining three, the most probable cause was the dilatation of the aortic ring.

Warthin [7] is of the opinion that congenital myocardial syphilis may lead later in life to the fibroid heart. He [8] also mentions myocardial atrophy and fibrosis as one of the causes of death in cases of cardiac failure. He considers myocardial atrophy and fibrosis due to slowly progressive mild syphilitic lesions the most common cause of cardiac failure in cardiac syphilis. Herxheimer [5] describes the syphilitic myocardial involvement as being of two types: the fibrous, which is more common, and the gummatous, which is rare. The latter is generally associated with the fibrous proliferative type. Brooks,[9] in a study of fifty hearts in cases of syphilis, found the myocardium injured to a serious degree in forty-four. The injury most frequently observed is an inflammatory process showing foci of fibrosis and small round cells about the arterioles.

Gross areas of slight myocardial fibrosis were noted in one of the twenty-eight hearts. In this heart there was also slight coronary thickening of the senile type. Microscopic fibrotic areas were seen in eleven of the twenty-eight hearts. The fibrosis was present in a slight degree in all but one, in which it was of a moderate degree. The left coronary in this case showed a severe amount of senile sclerosis. The type of fibrosis was purely atrophic in eight of the eleven positive cases. It consisted of atrophy of muscle fibers with replacement by scar tissue without the presence of leukocytes. This atrophic type of fibrosis is the kind commonly found in old people with coronary injury. In three of these eight, slight gross injury was noted in the coronaries. In three cases, the fibrosis was proliferative and of a slight degree and might easily have been syphilitic in origin.

It appears evident that, aside from the hypertrophy, little significance should be attached to the gross or microscopic anatomic changes observed in the myocardium of the twenty-eight hearts. Most of the small fibrotic areas were evidently a result of slight nonsyphilitic coronary injury, and were not of a sufficient degree to be a factor in heart failure. Syphilis of the myocardium in these twenty-eight hearts

with aortic insufficiency was apparently rare and when present was of an insignificant degree.

The importance of finding spirochetes in the heart has been emphasized by Warthin.[10] In a study of 200 hearts, he found the spirochetes by the Levaditi method. He also found spirochetes in five cases with myxedematous growths in the heart and in the heart muscle in eight cases in which death occurred suddenly.

Ten blocks from various parts of the heart of each of the twenty-eight patients were stained for spirochetes by the Levaditi method. With each group of material a tissue known to be syphilitic was stained as a control. This control material in every case showed many spirochetes, but spirochetes could not be found in any of the twenty-eight hearts having syphilitic aortic insufficiency. Herxheimer [5] referred to the presence of syphilitic pericarditis in association with syphilitic aortitis, but considered it of less frequent occurrence than syphilitic endocarditis. He believed that the pericarditis was an extension from the myocardium.

In the twenty-eight hearts showing aortic insufficiency, pericarditis was noted in three. The pericardial sac was obliterated by fibrous adhesions in two of these. Lymphocytes were found in the epicardium of one of these two hearts. In the heart which did not show a gross pericarditis, proliferative inflammation with lymphocytes was seen in the epicardium. Pericarditis was not a characteristic condition with syphilitic aortitis in this group of twenty-eight hearts.

Various conditions have been mentioned as the cause of death in cardiac syphilis. Warthin [8] states that old latent syphilis is one of the most important, if not the most important cause leading to myocardial insufficiency, and that patients with latent syphilis, in the great majority of cases, eventually die of cardiac failure, which may be brought about in several ways: myocardial atrophy and fibrosis, syphilitic disease of the coronaries with resulting infarction and fibrosis, syphilis of the aortic valve which is always associated with some degree of myocardial syphilis or an acute exacerbation of a previously latent syphilis. In this report the weight of the hearts is not given. Scott,[4] in all of his twenty-five cases, noted injury to the aortic valve with resulting hypertrophy.

With the exception of the hypertrophy, we found no evident anatomic change in the myocardium which seemed sufficient to cause death. The gross and microscopic injuries were of little significance. In practically all cases the process clearly seemed to be an aortic insufficiency resulting from a marginal thickening and shortening of the aortic cusps or a

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10. Warthin, A. S.: Primary Tissue Lesions in the Heart Produced by Spirochaete Pallida, Am. J. Med. Sc. **147**:667, 1914; ibid. (footnotes 7 and 8).

separation of the aortic attachments of the cusps. Hypertrophy followed, as it does in aortic insufficiency of rheumatic origin. It is a well known fact that hearts regularly fail without anatomic myocardial evidence, when hypertrophy has reached such a stage that the heart weighs 500 Gm. or more. The partial or complete closure of the coronary orifices must also have a part in producing failure. The two conspicuous anatomic causes of cardiac failure in this group were: hypertrophy resulting from a cordlike thickening and shortening of the free margin of the aortic cusps or a separation of the attachments of the aortic cusps to the aorta, and narrowing of the coronary orifices. Myocardial failure with syphilitic aortic insufficiency and passive con-

TABLE 2.—*Narrowing of Coronary Orifices*

Age	Sex	Marginal Thickening	Separation of Cusps	Left Coronary Orifice	Right Coronary Orifice	Distal Left Coronary	Distal Right Coronary	Weight of Heart	Gross Myocardial Fibrosis	Microscopic Myocardial Fibrosis	Reaction in Myocardium	Pericarditis: Old	Pericarditis: Acute	Pericarditis: Microscopic	Spirochetes
51	M	+	+	1/10	¾	+	—	360	—	—	—	—	—	—	—
63	F	—	—	¼	¾	—	—	275	—	—	—	+	—	—	—
43	M	—	—	¼	¾	—	—	395	—	—	—	—	—	—	—
62	M	+	+	¼	¾	—	—	350	—	—	—	—	—	—	—
49	M	—	—	⅛	—	—	—	435	—	++	p	—	—	—	—
35	F	—	—	½	O	+	—	385	—	+ b	p	—	—	—	—
35	M	—	—	⅛	O	—	—	415	—	—	—	—	—	—	—
44	M	—	—	⅝	¾	—	—	400	—	—	—	—	—	—	—
42	F	—	—	½	⅝	+	+	375	—	+	p & L	—	—	—	—
39	M	—	—	1/10	½	—	—	305	—	—	—	—	—	—	—
31	M	—	—	O	½	—	—	360	—	—	—	—	—	—	—
58	F	—	—	⅛	½	—	—	280	—	+ b	p & L	—	—	—	—
30	F	+	+	O	½	—	—	315	—	—	—	—	—	—	—
35	M	—	—	O	½	—	—	395	—	—	—	—	—	—	—
34	M	+	+	O	¾	—	—	600	—	—	—	—	—	—	—
		4	4			3	1			4					

gestion of the liver is apparently similar to myocardial failure with aortic insufficiency of other origins.

SUDDEN DEATH FROM CLOSURE OF CORONARY ORIFICES

Twenty-five of the 126 patients died rather suddenly with no decided previous clinical symptoms. Fifteen of the twenty-five hearts were preserved for study. The closure of the coronary orifices was the conspicuous anatomic change observed in these hearts (table 2). Both right and left coronary orifices showed narrowing in all but one heart, and in this the left coronary orifice was reduced to one-eighth of its normal diameter. Four of the left coronary orifices showed complete closure, and the remaining eleven showed a reduction in diameter, varying from one-half to one-tenth of the normal. Two of the right orifices were completely closed, twelve were reduced from three-quarters to one-eighth of the normal diameter, and one showed no narrowing.

In three of the fifteen cases the left coronary arteries distal to the orifices showed a slight degree of thickening. In one of these three cases, the same degree of thickening was observed in the distal part of the right coronary artery. The character of this thickening was similar to that found in senile coronary sclerosis. As in the cases of aortic insufficiency, coronary disease in these fifteen hearts was rare, with the exception of the syphilitic involvement at the orifices.

Gross myocardial fibrosis was not observed in any of these fifteen hearts. Infarcts commonly found in cases of senile coronary sclerosis were not present in any of the hearts which had syphilitic narrowing of the coronary orifices. Microscopic myocardial fibrosis was seen in four of the fifteen hearts, three times in a slight degree and once in a moderate degree. The scars in all four cases were proliferative with lymphocytic infiltration. Old pericarditis was noted in one case. The infrequency of fibrosis and the slight degree when it is present lead one to think that the anatomic myocardial condition has little or nothing to do with cardiac failure in these hearts.

Ten blocks from each of thirteen of these fifteen hearts were stained for spirochetes, using a known control. Spirochetes were not found in any of the thirteen hearts. Cordlike thickening of the free margin of the aortic cusps and a separation of the aortic attachments of the cusps were present in four of the fifteen hearts.

Hypertrophy was much less conspicuous in this group than in the hearts with aortic insufficiency. One heart weighed 600 Gm. The valvular injury in this heart was sufficient to produce the hypertrophy. Of the twenty-five hearts, the largest heart of a man weighed 600 Gm., the smallest 305 Gm., and the average weight was 420 Gm. The largest heart of a woman weighed 440 Gm.; the smallest, 140 Gm., and the average weight was 316 Gm. While there was some hypertrophy in this group of hearts, in most cases it apparently has little to do with bringing about the sudden death. Death evidently results primarily from the narrowing of the coronary orifices. Some of these cases, no doubt, would have gone on to aortic insufficiency, had death not resulted from coronary narrowing.

RUPTURE OF SYPHILITIC AORTIC ANEURYSM

Thirty-five of the 126 patients with cardiac syphilis died from a rupture of an aneurysm. Of these thirty-five cases, twenty-three hearts were preserved. Valvular injury was present in four of the twenty-three hearts, three times as both free marginal thickening and separation of the attachments of the cusps and once with marginal thickening alone (table 3).

The weight of the heart was recorded in twenty-six of the thirty-five cases. As in the group with coronary narrowing, the hypertrophy was

less than in the group with aortic insufficiency. The largest heart of a man recorded weighed 650 Gm.; the smallest, 285 Gm., and the average weight was 357 Gm. The weight of the heart of only one woman was recorded; it was 200 Gm.

The coronary orifices showed narrowing in three of the twenty-three cases, once in the left orifice with narrowing to one-quarter the normal diameter and twice in the right orifices with reduction to three-quarters the normal diameters. The coronary arteries showed a slight distal thickening in one case.

TABLE 3.—*Rupture of Aortic Aneurysm*

Age	Sex	Marginal Thickening	Separation of Cusps	Left Coronary Orifice	Right Coronary Orifice	Distal Left Coronary	Distal Right Coronary	Weight of Heart	Gross Myocardial Fibrosis	Microscopic Myocardial Fibrosis	Reaction in Myocardium	Pericarditis: Old	Pericarditis: Acute	Pericarditis: Microscopic	Spirochetes
40	M	—	—	—	—	—	—	...	—	+ b	p	+	—	—	—
57	M	—	—	—	—	—	—	...	—	—	—	—	—	—	—
48	M	—	—	—	—	—	—	350	—	—	—	—	—	—	—
59	M	—	—	—	—	—	—	350	—	—	—	—	—	—	—
50	M	+	+	—	—	—	—	375	—	—	—	—	—	—	—
55	M	—	—	—	—	—	—	300	—	—	—	—	—	—	—
42	M	—	—	—	¾	—	—	200	—	—	—	—	—	—	—
58	M	—	—	—	—	—	—	320	—	—	—	—	—	p & L	—
64	M	+	—	—	—	—	—	350	—	—	—	+	—	L	—
48	F	+	+	—	—	—	—	...	—	—	—	—	—	—	—
62	M	—	—	—	—	—	—	350	—	—	—	—	—	—	—
39	M	+	+	—	—	—	—	650	—	—	—	—	—	—	—
51	M	—	—	—	—	—	—	300	—	+ b	L	—	—	—	—
52	M	—	—	—	—	—	—	200	—	—	—	—	—	L	—
45	M	—	—	—	—	—	—	340	—	+ b	p	—	—	—	—
56	M	—	—	—	—	—	—	375	—	—	—	—	—	—	—
58	F	—	—	—	—	—	—	200	—	—	—	—	—	L	—
56	M	—	—	—	—	—	—	350	—	—	—	—	—	—	—
46	M	—	—	¼	—	—	—	...	—	—	—	—	—	—	—
46	M	—	—	—	¾	—	—	465	—	—	—	—	—	—	—
55	M	—	—	—	—	—	—	360	—	—	—	—	—	—	—
40	M	—	—	—	—	—	—	310	—	—	—	—	—	—	—
61	M	—	—	—	—	—	—	...	—	+ b	p & L	+	—	L	—
		4	3							4		3			

Gross myocardial fibrosis was not present in any of the twenty-three hearts. Fibrosis was present microscopically to a slight degree at the base about the ring in four of the twenty-three hearts, and was proliferative with lymphocytic infiltration. Spirochetes were sought in twenty-two of these hearts, as in the preceding groups, but none was found.

The cause of death in this group was obvious, but it is to be noted that the myocardial injury from inflammation was slight and was about the same as that found in the hearts with aortic insufficiency or in those with narrowing of the coronary orifices.

MULTIPLE GUMMAS OF THE MYOCARDIUM

Only three of the 126 patients showed gummas in the myocardium (table 4); these died suddenly. The left coronary orifice showed a

narrowing to three-quarters of its diameter in one heart. Typical gummas surrounded by proliferating fibroblasts and lymphocytes were present in the three hearts. In one there were many giant cells. Gross and microscopic evidence of pericarditis was present in one. One heart was that of a woman, and it weighed 442 Gm. The other two were hearts of men, and weighed 495 Gm. and 400 Gm. Spirochetes were not found in any of these. Death evidently resulted from anatomic myocardial injury.

MISCELLANEOUS GROUP

A miscellaneous group includes seventeen cases of syphilitic aortitis which were found accidentally at necropsy (table 4). Death resulted from the following causes: coronary sclerosis with thrombosis, two;

TABLE 4.—*Gummas of Myocardium*
Miscellaneous Group

Age	Sex	Marginal Thickening	Separation of Cusps	Left Coronary Orifice	Right Coronary Orifice	Distal Left Coronary	Distal Right Coronary	Weight of Heart	Gross Myocardial Fibrosis	Microscopic Myocardial Fibrosis	Reaction in Myocardium	Pericarditis: Old	Pericarditis: Acute	Pericarditis: Microscopic	Spirochetes
35	F	—	—	—	—	—	—	442	++++	++++	p & L	+	—	L	—
28	M	—	—	¾	O	—	—	495	++++	++	p & L	—	—	—	—
32	M	—	—	—	—	—	—	400	++++	+++	p & L*	—	—	—	—
								Miscellaneous Group							
42	M	—	—	—	—	+++ t	+	350	—	++	a	—	—	—	—
56	M	—	—	—	—	—	—	...	—	—	..	—	—	L	—
63	M	—	—	—	—	—	—	...	—	+	a	—	—	—	—
43	M	—	—	—	—	—	—	535	—	—	..	—	—	—	—
40	M	—	—	—	—	++++	—	340	—	—	..	—	—	—	—
47	M	—	—	¼	—	+	++	360	—	+	a	—	—	—	—
32	F	—	—	—	—	—	—	275	—	—	..	—	—	—	—
34	M	—	—	—	—	—	—	425	—	—	..	—	—	—	—
32	F	+	—	—	—	— t	—	310	—	—	..	—	—	—	—

carcinoma of the pancreas, one; carcinoma of the esophagus, one; carcinoma of the lung, one; lobar pneumonia, two; bronchopneumonia, two; pernicious anemia, one; cerebral hemorrhage, one; cerebrospinal syphilis, one; automobile accident, two; abortion, one; acute alcoholism, one; murder, one. Nine hearts were preserved. In one of these there was a marginal thickening of the aortic cusps. The left coronary orifice in one case showed narrowing to one-quarter of the normal diameter. The distal part of the left coronary artery showed a severe degree of thickening in three cases, with thrombosis in two. One right coronary artery showed a moderate degree of thickening in its distal part.

Gross myocardial fibrosis was not noted in this group. Microscopic myocardial fibrosis was present in three of the nine hearts, once in a moderate degree and twice in a slight degree. The character of the fibrosis was atrophic in all. Evidence of microscopic pericarditis was

present in one. Hypertrophy was not marked in this group, but was present. The largest heart of a man weighed 535 Gm.; the smallest, 220 Gm., and the average was 381 Gm. The largest heart of a woman weighed 275 Gm.; the smallest, 240 Gm., and the average was 257 Gm.

The problem in these cases of syphilitic aortitis narrowed itself to an explanation of the cause of death. The seventeen cases in which syphilitic aortitis was accidentally found at necropsy need no discussion. Likewise, the immediate cause of death was obvious in the three cases with multiple gummas of the myocardium and in the thirty-five cases with a rupture of an aortic aneurysm.

The primary causes of death in most cases of syphilitic aortitis, aside from a rupture of an aortic aneurysm, are valvular injury with insufficiency and narrowing of the orifices of the coronary arteries. The valvular injury is a valvulitis, which appears to be characteristic of syphilis, or a proliferation of the intima of the aorta with a separation of the aortic cusps at their attachment to the aorta. In none of the hearts examined did the myocardial injury indicated by fibrotic areas or any other anatomic change appear sufficient to account for the cardiac failure.

In the group with aortic insufficiency the myocardial hypertrophy was as great as that found in hypertensive hearts, and the cause of death, as in the hypertensive hearts, was evidently myocardial exhaustion. The hypertrophy was accounted for in most cases by the diseased aortic valve, by free marginal thickening with shortening or wrinkling and by a separation of the attachment of the aortic cusps. In the three cases without aortic valvular deformity, the insufficiency probably followed a stretching of the aortic ring. Narrowing of the coronary orifices was no doubt also a factor in helping to bring about death in many of this group. In the absence of serious gross or microscopic injury to the myocardium or to the coronary arteries distal to their orifices, it seems possible to consider the myocardial failure in the forty-six cases in group 1 as chiefly a result of the aortic valvular injury with insufficiency.

In the twenty-five cases in group *2*, in which death occurred suddenly, the only factor of importance in producing death, with the exception of a slight valvular involvement in a few cases, seems to have been the narrowing of the coronary orifices. Little injury was observed in the coronaries distal to their orifices or in the myocardium or pericardium, but there was a marked narrowing of the coronary orifices.

CONCLUSIONS

Syphilitic valvulitis is commonly associated with syphilitic aortitis. The gross appearance of the valvulitis (a cordlike thickening of the free margins) seems to be characteristic for syphilis. Microscopically, the inflammation is proliferative at first, but soon the inflammatory

areas undergo hyalinization, with the formation of a scar. The gross injury to the aortic cusps regularly produces insufficiency, but never stenosis.

Another common cause of aortic insufficiency is an intimal proliferation in the aorta, resulting in a separation of the aortic cusps at their attachments to the aorta.

Narrowing of the coronary orifices to the extent of producing death is common.

Coronary injury distal to the orifices and anatomic myocardial or pericardial injury in acquired syphilis appear to be of little significance.

Myocardial hypertrophy, as in other forms of aortic insufficiency, is common.

Except in the cases with rupture of an aortic aneurysm and in the few cases with multiple gummas of the myocardium, death practically always appears to have been caused by the aortic valvular injury with insufficiency or by the narrowing of the orifices of the coronary arteries.

Sudden death with syphilitic aortitis is rarely due to a myocardial inflammatory condition.

THE PERIAORTIC FAT BODIES*

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I shall describe briefly certain masses of fat within the pericardium which I call "the periaortic fat bodies." No doubt they have been observed by others, but little attention has been given to them. Only a limited number of animals have been examined in the study of these structures, but observations are now being made on a larger variety of animals.

Within the pericardium near the base of the heart of the adult dog are masses of fat which bear a definite relation to the ascending aorta. When the pericardium is opened, it is seen that these masses lie about the large vessels ventrally and fill the space beween the auricular appendages (fig. 1). Close examination shows that they are distinct bodies. One lies in or near the groove between the pulmonary artery and the aorta. It extends toward the base of the heart and is usually continuous with the fat on the heart proper. Another begins near the attachment of the pericardium to the large vessel and extends downward to the left. It lies in front of the aorta and runs transversely, usually terminating a little to the left of the median line of the aorta. A third fat body lies well to the left and posterior to the aorta. It extends from the attachment of the parietal pericardium posteriorly toward the opening of the transverse sinus, and often enters and terminates in this channel.

These bodies look like fat, and are whitish pink. They are roughly from 1 to 3 cm. long, from 1 to 2 cm. wide and from 0.5 to 1 cm. deep, depending on the size of the dog. They have tonguelike processes, which are intimately attached to the adventitia of the large blood vessels beneath, often giving the appearance of somewhat flattened, pedunculated masses. The surface may be filled with grooves and fissures, which divide the body into irregular lobules. The attachment of the prominent anterior fat body is about 1 cm. above the heart on the aorta, and is usually distinct from the fatty part of the cardiac musculature.

They are found uniformly in all adult dogs. Their position, location, form and size are constant. They receive a supply of blood both from the pericardium, from which a small vessel penetrates their upper portion, and from vessels from the wall of the aorta.

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The bodies are not developed in a new-born puppy. Close examination of the aorta reveals a small amount of loose fibrous tissue, containing a small amount of fat, which may be readily overlooked. These bodies are well developed and prominent in a puppy 4 weeks old. Roughly, they are about one-half the size of the fat bodies in adult dogs.

There seems to be little relation between the amount of fat present in the animal and the size or appearance of these bodies of fat. In

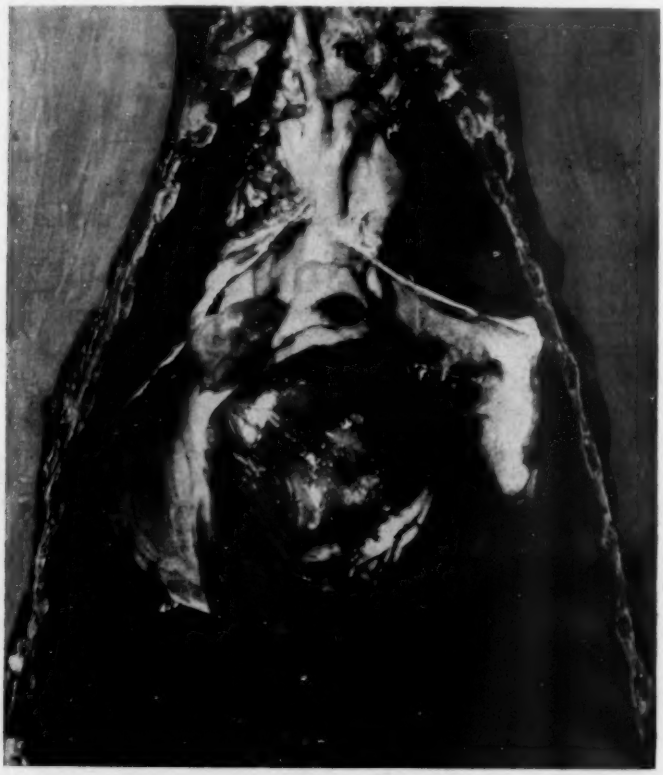

Fig. 1.—Dog's heart showing periaortic fat bodies about the aorta containing a mass of thyroid tissue.

new-born puppies, which contain a large amount of fat, these bodies are either not present or are undeveloped. In emaciated dogs, in which the amount of general body fat is small, they are nearly as prominent as in fat animals.

Small reddish-brown bodies are often seen immersed in the fat bodies. When examined under the microscope, these are seen to consist of thyroid tissue. There may be one or several; they may appear prominently on the surface or may be well covered by fat. In a series of fifty adult dogs, they were found by gross examination in 22, or 44

per cent. They vary from the size of a pinpoint to 1 cm. or more across. No doubt serial sections would reveal a larger percentage. They are chiefly found in the anterior and posterior bodies. Microscopic section shows that some are definitely encapsulated; others are embededd in the fat and do not have a capsule. They are rich in colloid and are supplied with blood by rather large, prominent vessels, often by one at each end. The acini are uniform in size and are lined by typical normal thyroid cells.

Histologically, the fat bodies possess the structure of ordinary fat and are covered with a layer of typical pericardial tissue. Numerous

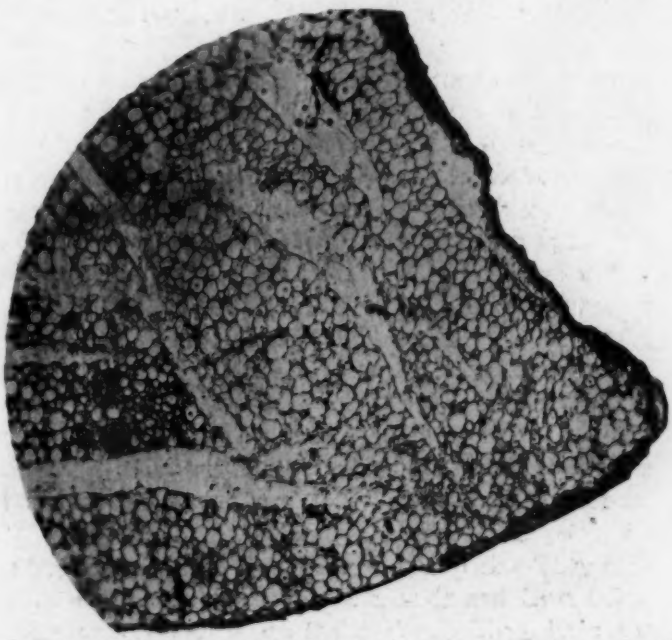

Fig. 2.—Microscopic section of fat body in dog with enveloping pericardium.

small blood vessels are seen in the fat, which appears to be of the ordinary glycerine-ester type when specifically stained.

It was noted in a number of dogs having enlarged thyroid glands that the intrapericardial thyroid bodies were also large, and microscopic examination showed distinct evidence of hypertrophy.

Similar bodies are found in the same location in the cat, but with a more ringlike arrangement about the aorta. They are of about the same relative prominence as in the dog. The surfaces are often lobulated. The left body runs along the pulmonary artery and fuses anteriorly with the middle fat body. The latter is prominent on the left side of the aorta, where there is often a relatively large mass of fat. As in the dog, the body on the right is near, or projects into, the trans-

verse sinus. Thyroid bodies were not found in the gross examination of twelve specimens. They may have been present, but of microscopic size. In new-born kittens, the fat bodies are entirely undeveloped; they are distinctly formed in kittens from 3 to 4 weeks old, and are about one-half the size of the adult body.

These bodies do not appear in as typical form in the hog as in the dog and cat. There is a finger-like extension of fat from the pericardium downward on the aorta, which is roughly 2 cm. long, 0.5 cm. wide and

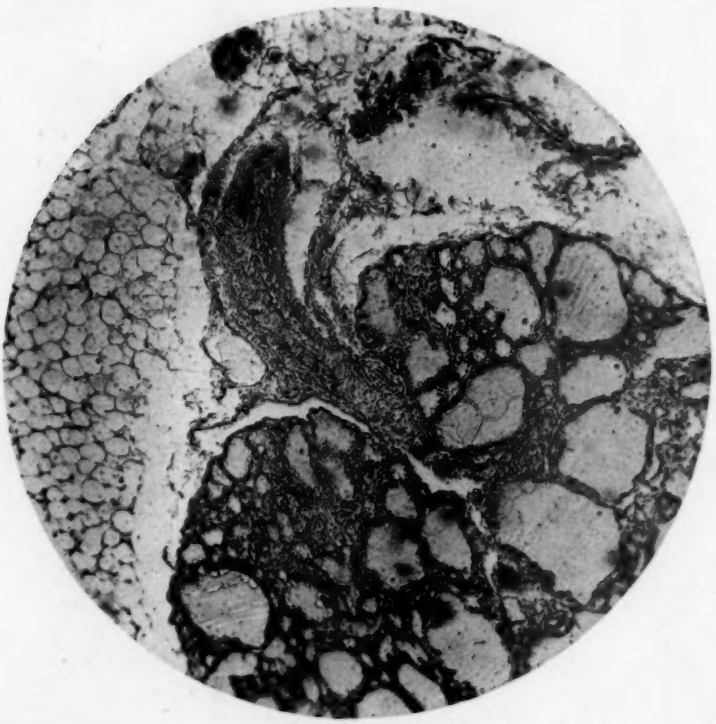

Fig. 3.—Section revealing thyroid tissue in a periaortic fat body in a dog, with abundant supply of blood.

about 0.25 cm. deep, and which is possibly analogous to the middle body. In the groove, between the aorta and the pulmonary artery, is an irregular small mass which fuses anteriorly with the middle fat body. The other fat body is on the right side, posterior to the aorta and near the transverse sinus. It is usually small and irregular. In fifteen specimens examined grossly, evidence of thyroid tissue was not found in these masses of fat.

Fat bodies have much the same appearance in the sheep as in the hog. Two finger-like processes project downward along the aorta.

The structures are not ringlike, as in the cat or dog. The right posterior body of fat tissue is found at the entrance to the transverse sinus. Evidence of thyroid was not found in fifteen specimens on gross examination.

It is difficult to make out definite bodies in the cow. There are irregular thin masses of fat about the aorta and between the aorta and the pulmonary artery, with here and there patches of whitish fibrous tissue. Thyroid tissue was not seen on gross examination in fifteen specimens.

Likewise it is difficult to make out bodies in the rat, mouse, guinea-pig and rabbit that one can correlate with the fat bodies of the cat and dog. At a corresponding location about the aorta one sees a little fibrous tissue containing a small amount of fat, but it does not form definite bodies. Thyroid tissue has not been observed in the relatively small number of specimens thus far examined.

On and partly encircling the aorta of the human being, there is at times an indefinite ringlike elevation about 0.5 cm. wide and about 2 cm. above the base of the heart. On or near this are small, thin masses of fat, apparently in the adventitia. The question as to whether these structures are analogous to the fat bodies of other animals is undetermined. The human being more closely resembles the cow than the other animals examined.

Thyroid bodies were observed long ago about the arch of the aorta in the dog. Wölfler [1] noted the presence of thyroid tissue in this location and referred to it as aortic glands. Evidently no special attention was given to the fat bodies in which the aberrant thyroids were found, though he speaks of "Fettlüppchen" lying in this region.

Swarts and Thompson,[2] under the title of "Aberrant Thyroids in the Pericardium in the Dog," described thyroid tissue within the pericardium in connection with masses of preaortic fat. No doubt this fat is the same as the fat bodies described, though the authors do not give a detailed description of it. They found thyroid tissue within the pericardium in twenty-four of thirty dogs. They also noted definite goiter changes in the pericardial thyroid tissue of dogs having enlarged thyroid glands.

Woodruff,[3] in a recent paper on studies on the vasa vasorum, refers to and shows by illustration pads of fat which assume bizarre shapes and fill spaces between the auricles. The fat was deeply colored in his injection preparations, indicating an abundant blood supply.

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1. Wölfler: Wiener med. Wchnschr. **29**:198, 1879.
2. Swarts and Thompson: Aberrant Thyroids in Pericardium in the Dog, J. M. Research **24**:299, 1911.
3. Woodruff, C. E.: Studies on the Vasa Vasorum, Am. J. Path. **2**:567, 1926.

SUMMARY

In certain animals characteristic fat bodies with a definite morphology constantly occur about the aorta. Of the animals examined, the dog and the cat reveal such structures in most striking form. Aberrant thyroid tissue often occurs in the fat bodies in the dog. Thyroid tissue has not yet been found in other animals, though microscopic serial sections must be made to determine this point.

The frequent presence of thyroid tissue in the fat bodies indicates that they probably originate high up in the neck and migrate downward during early development. This would mean that the fat bodies are probably introduced from a distance and are not simply local accumulations of fat. This is also supported by the fact that in emaciated animals the fat bodies are not materially smaller than normally.

These bodies are undeveloped in new-born dogs and cats. In three or four weeks they are well formed and about one-half normal size.

It is important to recognize the possible presence of these intrapericardial thyroid bodies in the dog in all experiments involving thyroidectomy, and to study carefully the embryology of the thyroid of the dog and of other animals.

The intrapericardial thyroid bodies in dogs afflicted with goiter may also be hypertrophied, undergoing the same changes as does the main thyroid gland.

THE SPHINCTER OF THE CHOLEDOCHUS *

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For several years, one of us (Mann) has studied anatomically the intramural portion of the common bile duct, and physiologically the discharge of bile into the duodenum, for the specific purpose of determining whether there is a sphincteric mechanism at the duodenal end of the choledochus. Reports of a few of these studies have been published, but for the most part they have remained unfinished on account of the difficulty of obtaining convincing data. While these studies were in progress, a great deal appeared in the literature both for and against the view that a sphincter exists and that it is of considerable clinical importance. In this article we shall review briefly the evidence for and against the presence of a sphincter, and present in a general way our own observations on the subject, attempting to indicate, on the basis of present knowledge, the clinical application that can logically be made. Although the data now available do not permit many positive statements concerning the sphincter of the choledochus, we wish to call attention to certain possible factors in the cause of symptoms and unsatisfactory postoperative results in one of the most important regions of the body.

THE ANATOMY OF THE SPHINCTER

It has been suggested that Glisson [1] suspected the existence of a sphincter of the choledochus which he thought would be necessary to prevent a reflux from the duodenum into the bile duct, but Gage [2] was the first to describe such a structure. He observed it in the cat, describing muscle fibers passing around the bile duct, around the pancreatic duct, and around both ducts. The first comparative study of the anatomy of the sphincter was made by Oddi,[3] who observed the duodenal

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* Read before the Section on Physiology and Pathology at the Seventy-Eighth Annual Session of the American Medical Association, Washington, D. C., May 16-20, 1927.

* From the Division of Experimental Surgery and Pathology, The Mayo Foundation.

1. Glisson, quoted by Oddi.

2. Gage, S. H.: The Ampulla of Vater and the Pancreatic Ducts in the Domestic Cat (Felis domestica), Am. Quart. Micr. J. **1**:126, 1879.

3. Oddi, Ruggero: D'une disposition à sphincter spéciale de l'ouverture du canal cholédoque, Arch. ital. de biol. **8**:317, 1887; Sulla tonicità dello sfintere del coledoco, Arch. per le sc. med. **12**:333, 1888.

portion of the common bile duct grossly and histologically in man, the dog, sheep, ox, pig, cat, horse, domestic pigeon, common fowl and guinea-fowl. He found that the course of the duct through the wall of the duodenum differs in the various species of animals. The arrangement of the smooth muscles around the duct likewise differs. In each species studied he noted a definite sphincter at the duodenal end of the common bile duct. Hendrickson [4] studied the biliary tract in the rabbit, in the dog and in man grossly and microscopically, and describes a definite sphincter of the common bile duct in each of these species. Helly [5] studied the intramural portion of the common bile duct in man and found a sphincter not only around the common bile duct but also around the duct of Wirsung, and a knitting together of the two into a more or less common whole. One of us (Mann) [6] studied the sphincter in ten species of animals possessing a gallbladder, and four species without a gallbladder. It was found that the course of the ducts through the duodenal wall and the arrangement of the muscle fibers around the ducts varied greatly. A definite arrangement of muscle fibers which might function as a sphincter was found in each species studied, although often the amount of muscle tissue was small. We [7] noted a group of muscle fibers that could act as a sphincter surrounding both the common bile duct and the pancreatic duct in man. Broman [8] has described a well-formed sphincter at the duodenal end of the common bile duct in a fetus of the antarctic whale. Auster and Crohn [9] were not able to demonstrate a distinct anatomic sphincter, although they described bands of smooth muscle passing around the intramural portion of the common bile duct in man and dog. Matsuno [10] describes an extensive layer of smooth muscle fibers around the common bile duct of man which is continuous at many points with the musculature of the intestinal tract, but differs from it in regard to the smallness of the fibers. The extramural portion

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4. Hendrickson, W. F.: A Study of the Musculature of the Entire Extrahepatic Biliary System, Including that of the Duodenal Portion of the Common Bile Duct and of the Sphincter, Bull. Johns Hopkins Hosp. **9**:221, 1898.

5. Helly, K. K.: Die Schliessmuskulatur an den Mündungen der Gallen und der Pankreasgänge, Arch. f. mikr. Anat. **54**:614, 1899.

6. Mann, F. C.: A Comparative Study of the Anatomy of the Sphincter at the Duodenal End of the Common Bile Duct, with Special Reference to Species of Animals Without a Gallbladder, Anat. Rec. **18**:355, 1920.

7. Mann, F. C., and Giordano, A. S.: The Bile Factor in Pancreatitis, Arch. Surg. **6**:1 (Jan.) 1923.

8. Broman, I.: Ueber die Phylogenese der Gallenblase, Upsala Läkaref. Förh. **26**:1, 1921.

9. Auster, L. S., and Crohn, B. B.: Notes on Studies in the Physiology of the Gallbladder, Am. J. M. Sc. **164**:345, 1922.

10. Matsuno, Y.: Ueber die Muskulatur des Ductus choledochus, Virchows Arch. f. path. Anat. **247**:208, 1923.

of the duct has only a few scattered muscle fibers, but at the sphincter the band of muscle is from 5 to 10 mm. wide. He believes that this is a true sphincter.

It would appear in most instances that observers found sufficient evidence to prove the existence of a sphincter. As pointed out in a previous review,[11] there is sufficient anatomic evidence to show that there is a bundle of muscles surrounding the termination of the common bile duct which could act as a sphincter. It is often difficult to find muscle fibers that encompass the duct exclusively, since they are so closely intermingled with the circular fibers of the intestine. Sometimes what would appear to be the sphincter is only an accentuation of the muscle coat in the intramural portion of the duct over that of the extramural portion, by the addition of fibers from the circular coat of the duodenum. The interlacing of the muscle fibers passing around the duct and the muscle fibers of the duodenum is often exceedingly intimate. Usually there are definite bundles which are distinct enough to be considered as a sphincter.

We have studied the intramural portion of the common bile duct in more than twenty species of animals. Our conclusions, as based on these studies, are the same as those deduced from the review of previous observations. It is usually possible to find a definite bundle of smooth muscles surrounding the common bile duct, contraction of which would tend to close the lumen. The amount of muscle tissue and its arrangement differ considerably in the various species and in individuals of the same species, and in many instances is very meager. In species in which the pancreatic duct opens with the common bile duct, a bundle of muscle fibers also embraces the former duct, and it appears that a contraction of this muscle would tend to close both ducts.

The intramural portion of the common bile duct in man has been studied especially. In some instances, the distal portion of the duct as it approaches the duodenum is covered anteriorly by a thin fold of pancreatic tissue until it enters the wall of the duodenum. In other instances, it runs in a sulcus on the surface of the pancreas. As the duct approaches the duodenum, it runs parallel with it for a short variable distance and then pierces the wall of the intestine, to open into its lumen on its posterolateral surface. The opening is usually represented by a longitudinal thickened fold pointing distally. Occasionally this fold is absent, only a small oval elevation being present. If the common bile duct is incised and its whole course through the duodenum is laid open, it is found that the so-called ampulla of Vater is a variable structure depending on the entrance of the duct of Wirsung into the duodenal

11. Mann, F. C.: The Functions of the Gallbladder, Physiol. Rev. **4**:251, 1924.

end of the common bile duct. As the duct enters the duodenum, it is surrounded by muscle fibers from the duodenum which reflect over the duct and intermingle with those of the common bile duct, thickening the wall of the intramural portion of the duct for a variable distance. This thickening does not extend around the orifice of the ampulla, but usually includes the pancreatic duct.

THE PHYSIOLOGY OF THE SPHINCTER

Only a few facts have been proved definitely with regard to the physiologic action of the sphincter. The usual physiologic method of determining whether there is a sphincter at the duodenal end of the common bile duct and the pressure it would withstand is as follows: A cannula is placed in the common bile duct pointing toward the orifice of the duct. A water or mercury manometer is connected to the cannula through a two-way tube. The wall of the duodenum is sectioned opposite the opening of the duct, exposing the papilla. Water or mercury is passed into the manometer until it appears in the aperture of the ampulla. The pressure just necessary to allow the fluid to flow into the duodenum is taken as a measure of the resistance of the sphincter. The procedure has been varied by leaving the duodenum intact and taking the residual pressure in the manometer after raising it above the point at which the fluid passes into the duodenum as the measure of the tone of the sphincter.

Oddi tested the tone of the sphincter by this method, and it withstood a maximal pressure of 50 mm. of mercury. Archibald [12] found that the sphincter of the dog withstood a pressure of from 180 to 330 mm. of water. One of us (Mann) [13] tested the residual pressure in the common bile duct in several species of animals and found a marked variation in the pressure, which seemed to measure the tone of the sphincter in the different species and in individual animals. The minimal pressures found were between 75 and 100 mm. of water. McWhorter [14] noted marked variation in the pressure withstood by the sphincter in dogs; in some animals it was as high as 580 mm. of water and in others as low as 30 mm. Jacobson and Gydesen [15] concluded that 150 mm. of water was about the maximal normal pressure withstood by the

12. Archibald, E.: The Experimental Production of Pancreatitis in Animals as the Result of the Resistance of the Common Duct Sphincter, Surg. Gynec. Obst. **28**:529, 1919.

13. Mann, F. C.: A Study of the Tonicity of the Sphincter at the Duodenal End of the Common Bile Duct, J. Lab. & Clin. Med. **5**:107, 1919.

14. McWhorter, G. L.: The Surgical Significance of the Common Bile Duct Sphincter, Surg. Gynec. Obst. **32**:124, 1921.

15. Jacobson, Conrad, and Gydesen, Carl: The Function of the Gallbladder in Biliary Flow, Arch. Surg. **5**:374 (Sept.) 1922.

sphincter. Winkelstein and Aschner [16] found that the sphincter withstood a pressure which was never less than 90 mm. of water and averaged from 120 to 130 mm. Burget [17] found a residual pressure in the common bile duct of from 2 to 13 mm. of mercury. Cole [18] found that the sphincter withstood a pressure of from 40 to 100 mm. of water. Copher and Kodama [19] found the residual pressure in the duct to vary from 50 to 250 mm. of water.

Many studies have been made of the action of various stimuli on the sphincter. Oddi discovered special ganglions in the region of the sphincter and postulated that it was under special control by the nerves and could be affected reflexly by stimulation. By causing irritation of the duodenal mucosa with different forms of stimuli, he was able to induce much greater resistance to the flow of fluid from the bile duct into the duodenum. Doyon [20] obtained changes in the tone of the sphincter by irritating the gastric mucosa and by other similar procedures. Archibald applied hydrochloric acid to the papilla and noted that pressure as high as 800 mm. of water might be withstood. Reach [21] completely isolated the common duct and immersed it in Ringer's solution. He obtained evidence of tone of the sphincter by the use of various drugs. Winkelstein and Aschner noted difference in the residual pressure in the common bile duct, on the application of various substances to the papilla. Cole noted that changes in the hydrogen ion concentration in the fluid around the papilla and also distention of the stomach caused a change in tonus of the sphincter. Burget [17] observed the effect of several of the more important drugs on the resistance offered to the passage of fluid from the common bile duct into the duodenum. He concluded that drugs that affect the tonus of the intestinal musculature affect the resistance and that the latter is due to the duodenal wall. Copher and Kodama obtained similar results.

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16. Winkelstein, A., and Aschner, P. W.: Experimental Studies on the Entrance of Bile into the Duodenum, Am. J. M. Sc. **169**:679, 1925; The Mechanism of the Flow of Bile from the Liver Into the Intestines, ibid. **171**:104, 1926.

17. Burget, G. E.: The Regulation of the Flow of Bile, Am. J. Physiol. **74**: 583, 1925.

18. Cole, W. H.: Relation of Gastric Content to the Physiology of the Common Duct Sphincter, Am. J. Physiol. **72**:39, 1925.

19. Copher, G. H., and Kodama, Shuichi: The Regulation of the Flow of Bile and Pancreatic Juice into the Duodenum, Arch. Int. Med. **38**:647, 1926.

20. Doyon, M.: Mouvements spontanés des voies biliares, Arch. de physiol. norm. et path. **5**:710, 1893; De l'action exercée par le systèm nerveux sur l'appareil excréteur de la bile, ibid. **6**:19, 1894.

21. Reach, Felix: Der Schliesmuskel des Ductus choledochus in funktioneller Beziehung, Arch. f. exper. Path. u. Pharmakol. **85**:178, 1920.

The problem of the sphincter of the choledochus is inseparable from the problem of the mechanism of filling the gallbladder, and that of the discharge of bile into the duodenum. An undebatable explanation of these is not at hand. It is clear that the liver secretes bile continuously, although at a varying rate, depending on dietetic and other factors, but the discharge into the duodenum is intermittent. It is also definitely established that in the fasting state, when the discharge of bile into the duodenum is least, the gallbladder is filled, but, after the ingestion of certain foods, it empties. Doyon noted a simultaneous relaxation of the sphincter and contraction of the gallbladder. Meltzer,[22] interested mainly in his conception of contrary innervation, postulated a reciprocal action between the gallbladder and the sphincter. A failure to understand Meltzer's point of view and the too literal interpretation of his assertions has undoubtedly retarded the accumulation of accurate data concerning the mechanism of the biliary tract. Whatever may be the final explanation with regard to the mechanism of filling of the gallbladder and that of the discharge of bile into the intestine, the view that there is a sphincter around the common bile duct which acts like a faucet in draining the gallbladder is certainly not correct. The emptying of the gallbladder is not necessarily dependent on any action of a sphincter of the choledochus, as was shown conclusively by Hamrick,[23] who inserted a tube into the intramural portion of the common bile duct and injected an opaque medium into the gallbladder. The medium remained in the gallbladder almost undiminished in amount for several days and until after a meal of egg-yolk and cream, when it was almost all forced into the duodenum. Such observations, however, do not necessarily mean that there is a reciprocal relationship between the sphincter of the choledochus and the gallbladder. As a matter of fact, the experiments of Rost,[24] Potter and Mann [25] and McMaster and Elman [26] on the intact animal strongly suggest such a relationship.

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22. Meltzer, S. J.: The Disturbance of the Law of Contrary Innervation as a Pathogenetic Factor in the Diseases of the Bile Ducts and the Gallbladder, Am. J. M. Sc. **153**:469, 1917.

23. Hamrick, R. A.: The Emptying of the Gallbladder; An Experimental Study, Am. J. M. Sc. **174**:168, 1927.

24. Rost, Franz: Die funktionelle Bedeutung der Gallenblase. Experimentelle und anatomische Untersuchungen nach Cholecystektomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:710, 1913.

25. Potter, J. C., and Mann, F. C.: Pressure Changes in the Biliary Tract, Am. J. M. Sc. **171**:202, 1926.

26. McMaster, P. D., and Elman, R.: On the Expulsion of Bile by the Gallbladder; and a Reciprocal Relationship with the Sphincter Activity, J. Exper. Med. **44**:173, 1926.

The discharge of bile into the duodenum has been interpreted differently in reference to the presence or absence of a sphincter. Bruno,[27] studying animals with duodenal fistula, observed that bile emerged from the intact ampulla intermittently. This seemed to indicate a sphincteric action. Rost has investigated this phase of the subject extensively. A specially constructed cannula in the duodenum of dogs made it possible to observe the discharge of bile from the papillar orifice. He noted that in the normal fasting dog bile was seldom discharged into the duodenum oftener than once an hour; a strong irritation was necessary to cause the discharge. Certain substances, notably peptone, would cause a gush of bile. This intermittent discharge was attributed to the opening of the sphincter of the common bile duct, and the expulsion of bile from the gallbladder. Klee and Klüpfel[28] repeated Rost's experiments and obtained almost identical results.

In most species of animals, the position of the gallbladder is such that it is difficult to understand how it could fill without the resistance to the flow of bile offered by the intramural portion of the common bile duct. If this portion of the duct is kept patent, the gallbladder will not fill, as shown by Winkelstein and Aschner and Whitaker.[29]

The observation of animals on which cholecystectomy had been performed has furnished evidence of a sphincteric mechanism controlling the discharge of bile. Judd and one of us (Mann)[30] observed the residual pressure in the common bile duct in such animals until dilatation of the extrahepatic biliary tract occurred and found the pressure greatly reduced. Winkelstein and Aschner made similar observations. Rost noted the discharge of bile in dogs in which cholecystectomy had been performed and permanent biliary fistula established, and found that the discharge after removal of the gallbladder varied in different animals and with the length of time after operation. There was more or less constant dribbling of bile into the duodenum immediately after operation. In some animals there was a return to the normal intermittent type of discharge; in others, the dribbling persisted indefinitely. Klee and Klüpfel obtained similar results. Potter and Mann noted an increase in the pressure in the common bile duct immediately after removal of the gallbladder.

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27. Bruno, G. G.: L'excitabilité spécifique de la muquese du tube digestif. Sixième mémoire. La bile comme agent digestif, Arch. sc. biol. **7**:87, 1899.

28. Klee, P., and Klüpfel, O.: Experimenteller Beitrag zur Funktion der Gallenblaze, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **27**:785, 1914.

29. Whitaker, L. R.: The Mechanism of the Gallbladder, Am. J. Physiol. **88**:411, 1926.

30. Judd, E. S., and Mann, F. C.: The Effect of Removal of the Gallbladder, Surg. Gynec. Obst. **24**:437, 1917.

Potter and Mann, realizing the many possible sources of error in attempting to determine the physiologic action of the sphincter in acute experiments, developed a method for studying the pressure changes in the biliary tract in the intact animal. This was accomplished by placing a rubber T tube in the common bile duct and a metal tube in the gallbladder. After both tubes had healed in position, the pressure changes in the two tubes were observed under various conditions. It was found that the pressure in the gallbladder and common bile duct was not necessarily the same and that both pressures fluctuated, depending on the diet. The pressure in the duct was low in the fasting animal and highest after a feeding of milk. Waves of pressure variations were found which could best be explained on the basis of an actively functioning sphincter.

Elman and McMaster [31] also studied the physiologic variations in resistance to the flow of bile to the intestine in intact animals. They severed the common bile duct and intubated each end. It was thus possible, after the tubes had healed in position, to observe the pressure produced in the biliary tract from the liver and the gallbladder, and also to determine the pressure necessary to cause fluid to pass from the common bile duct into the duodenum. In regard to the latter, they concluded that the escape of bile into the duodenum is under definite control and is markedly influenced by varying the physiologic conditions. The average resistance to fluid passing from the common bile duct into the duodenum in from four to twelve hours after a feeding was found to be from 160 to 200 mm. of bile pressure. After a fast of from twenty-four to seventy-two hours, this resistance was increased and a pressure of 300 mm. might be necessary to permit fluid to pass into the duodenum. Seeing and taking food produced a reflex suddenly lessening the resistance of flow to the intestine. Alkali also caused increased resistance, and acid caused decreased resistance. When McMaster and Elman studied the changes in pressure and bile flow from the tube draining the common bile duct, they obtained definite evidence of forceful contraction of the gallbladder following feeding and other procedures, and also evidence of a reciprocal action of the sphincteric mechanism controlling the discharge of bile. They attributed the sudden changes observed chiefly to the activity of the sphincter.

Attempts have been made to prove that a sphincter does not exist, by transplanting the common bile duct partially or completely. Burget,[32] using dogs, dissected down on the duct at a point just back of the papilla

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31. Elman, R., and McMaster, P. D.: The Physiological Variations in Resistance to Bile Flow to the Intestine, J. Exper. Med. **44**:151, 1926.

32. Burget, G. E.: The Regulation of the Flow of Bile: II. Effect of Eliminating the Sphincter of Oddi, Am. J. Physiol. **79**:130, 1926.

and severed the duct. An opening was then made in the mucosa and the proximal end of the duct turned into the lumen of the intestine. He found that the response of drugs in the rate of flow of fluid through the common bile duct was the same as in normal dogs. Berg and Jobling [33] severed the common bile duct at its point of entrance into the duodenal wall and transplanted it back into the duodenum. They found that the gallbladder of such animals could be visualized and that the shadow decreased following the feeding of a fat meal. In regard to these experiments, the location of the muscle bands described as the sphincter should be recalled. The sphincter has not been described as being at the orifice of the ampulla. In a large series of experiments in which the common bile duct was severed and reimplanted into the gastrointestinal tract, we found that a certain degree of stenosis of the duct at the site of implantation, with varying degrees of dilatation of the biliary tract, always occurred. All the methods described of transplanting the common bile duct have been employed, but it appears that if the opening into which the duct is placed is sutured sufficiently tight to prevent leakage of the duodenal contents, a certain degree of obstruction of the duct will occur. While the animal with a transplanted bile duct may live in apparently good health for several years, the biliary tract is not normal. The dilated biliary tract functions as a whole; there is general stasis throughout the extrahepatic system; the bile drains slowly—in the cases examined it drained apparently more or less continuously into the duodenum. One would anticipate that such a gallbladder would be visualized in the roentgenogram made before the concentrating activity had been too badly damaged.

The influence of the activity of the duodenal wall on the discharge of bile has been a moot question. Oddi appeared to believe that the tone of the intestinal musculature opposed the action of the sphincter. Helly was not able to determine whether the sphincter could contract of its own accord, independently from the activity of the intestinal musculature. Rost suggested that there was a true sphincter. Klee and Klüpfel noted that when the gastric contents were expelled into the duodenum as every peristaltic wave passed the pylorus, a flow of bile occurred. Potter and Mann were not able to correlate consistently the pressure waves noted in the common bile duct with peristaltic waves in the duodenum. Elman and McMaster concluded that there was a sphincter but that peristalsis affected the discharge of bile. Whitaker concluded that the activity of the duodenum was of importance in the discharge of bile. Burget, Copher and Kodama attributed to the tone

33. Berg, B. N., and Jobling, J. W.: The Effect of Division and Transplantation of the Common Duct upon Gallbladder Function, Proc. Soc. Exper. Biol. and Med. **24**:434, 1927.

of the duodenal musculature and the peristalsis the entire mechanism of the discharge of bile.

Higgins and one of us (Mann)[34] demonstrated by a simple experiment that there is enough muscle around the intramural portion of the bile duct and that on stimulation it will prevent the outflow of bile, even at pressures greater than the secretory pressure of the liver or that produced by the contraction of the gallbladder. They exposed the common bile duct and inserted a cannula pointing toward the duodenum. The duct was then dissected away from the duodenal wall, care being taken to remove all the muscularis of the duodenum which could be seen grossly and which could be removed without injury to the duct. The cannula was then connected with a pressure bottle containing Ringer's solution warmed approximately to body temperature. The bottle was suspended so that by raising or lowering it, the pressure of the outflow could be varied. The intramural portion of the duct was placed firmly on the points of an electrode. The warm Ringer's solution was allowed to pass through the isolated duct, and records were made of the rate of flow before and after stimulation of the intramural portion. It was found that a brief electrical stimulation on a restricted region of the duct would induce contraction which stopped the flow of fluid even though the pressure of the fluid might be greater than the secretory pressure of the liver. It was often possible to cause the muscle to go into a state of tonic contraction which might persist for many minutes. The area of the duct which responded to stimulation by inhibiting the flow of the fluid was restricted, and was situated at about the site of, or slightly proximal to, the entrance of the pancreatic duct.

That peristalsis, variation in tone and spasm of the duodenal wall would influence the discharge of bile has never been questioned. It is difficult to prove that such factors are the only or prime ones controlling the passage of bile into the duodenum, and there are several facts that militate against such a view, making it appear that a true sphincter is essential. The more important of these are the following:

The extrahepatic biliary tract of a species of animal with a gallbladder and those normally without a gallbladder do not show any significant difference in size or in capacity to hold bile. However, when the gallbladder is removed, these extrahepatic ducts usually dilate. If the discharge of bile into the duodenum is wholly due to variation in tone, peristalsis, etc., of the duodenal wall, the foregoing observations would indicate that there was some fundamental difference either in the activity of the duodenum or in the rate or quantity of bile secreted in

34. Mann, F. C., and Higgins, G. M.: A Physiologic Consideration of the Sphincter of the Ductus Choledochus, Proc. Soc. Exper. Biol. & Med. **24**:533, 1927.

the animals with a gallbladder as compared with those without. As both of these processes are general and fundamental, it would appear more logical to explain the differences found in the two groups of animals on the basis that a localized sphincteric mechanism was present and functioning in species with a gallbladder and not functioning in those without. Definite evidence that there is a difference in the mechanism of discharge of bile in the animal with a gallbladder and the one without is furnished by an experiment which can easily be performed. If an animal possessing a gallbladder, such as the guinea-pig, rabbit, cat or dog, is anesthetized, the duodenum located and the

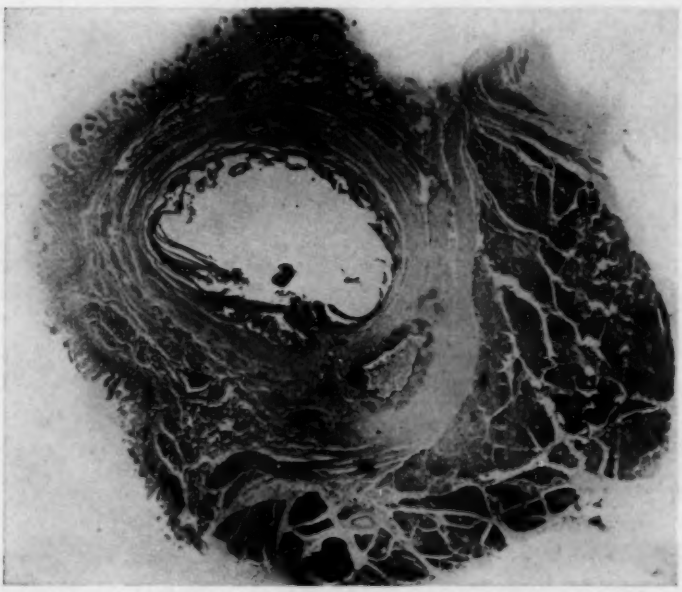

Fig. 1.—Section through the intramural portion of the common bile duct (Mann). The large amount of smooth muscle surrounding the bile duct as well as the pancreatic duct should be noted; × 6.

papillary orifice of the common bile duct exposed through a small opening opposite it in the duodenal wall, the bile may be easily seen discharging in intermittent spurts. It is usually possible to see the papillary orifice open and close. The bile and pancreatic juice may spurt from the orifice without any discernible peristalsis. However, if there are peristaltic waves in the duodenum, the outflow of bile will not occur except with the peristalsis. If the papillary orifice is gently irritated with a sponge, the outflow of bile may be inhibited for a considerable period and then may be discharged with a large spurt without producing any discernible change in the duodenal wall. If a rat, or a pocket gopher, a species normally without a gallbladder, is examined

in the same manner, different results will be found. The papilla is lacking in these species, and the bile flows continuously; the flow is never intermittent nor is the bile discharged in spurts. Sponging the opening of the duct does not inhibit the discharge. These observations definitely prove that there is a difference in the mechanism of discharge of bile into the duodenum in the two groups of animals, and this difference appears to be due to the presence of a sphincteric mechanism in one and not in the other.

This review of the work on the sphincter of the choledochus emphasizes several pertinent facts. It is obvious that most of the

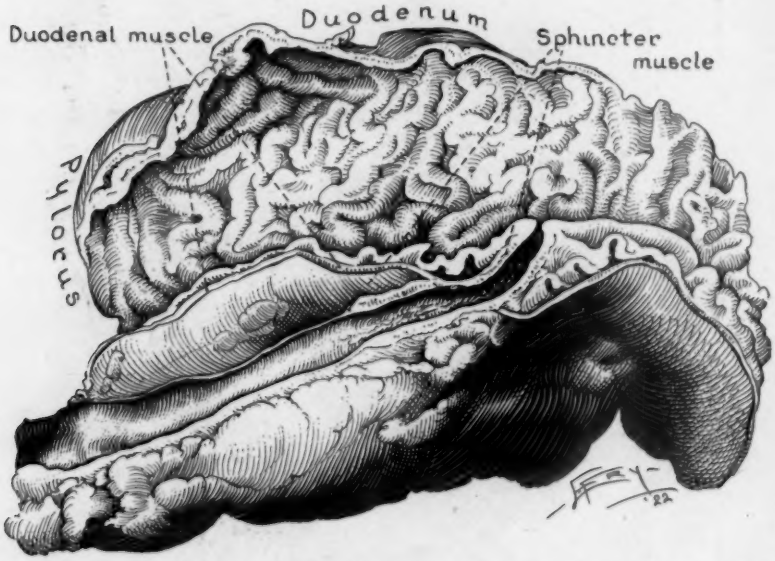

Fig. 2.—The duct-bearing portion of the duodenum in a case of cholecystitis, showing the increase in muscle around the common bile duct.

experiments were performed under conditions which might give rise to several kinds of error. Observations that were carried out on the intact animal are more free from criticism. It is evident that there is a mechanism at the duodenal end of the common bile duct which has to do with the discharge of bile into the intestine and the filling of the gallbladder. This mechanism is affected by environmental factors and food and probably by nerve reflexes. Whether this mechanism consists of a true sphincter, and whether it is dependent wholly on the activity of the musculature of the duodenal wall or both, has not been established. More suggestive evidence is that a true sphincter exists, rather than that the control of the discharge of bile depends only on the action of the duodenal wall.

THE RELATION OF SPHINTERIC MECHANISM TO PATHOLOGIC CONDITIONS IN ADJACENT ORGANS

A conception of a sphincter at the duodenal end of the common bile duct has formed a pertinent part in the conception of the cause of certain pathologic conditions. Oddi suggested that certain types of

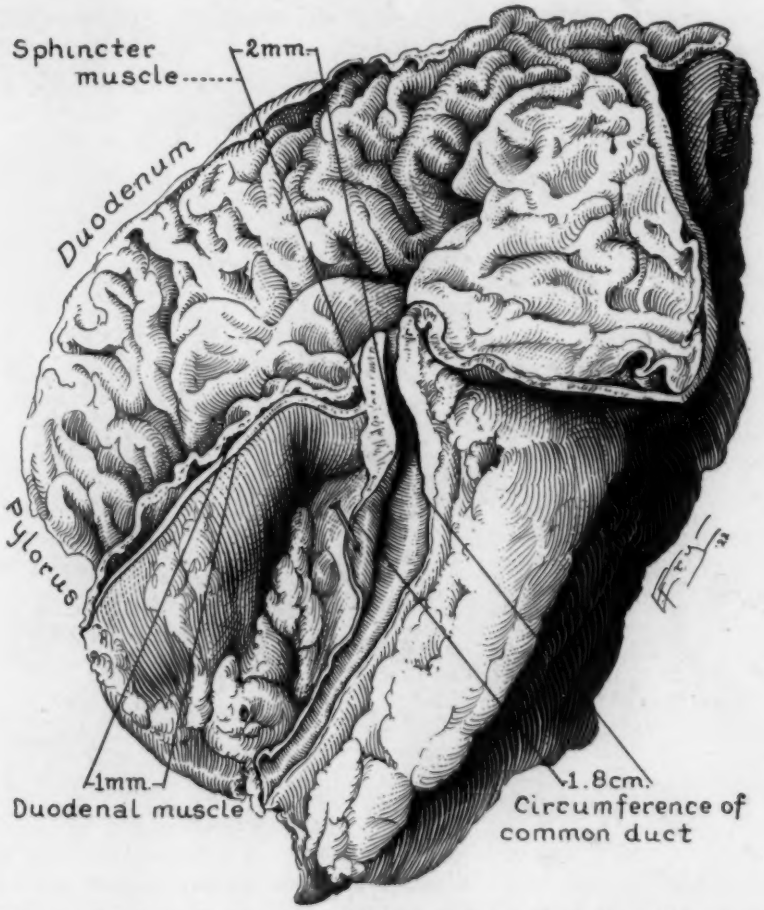

Fig. 3.—Specimen similar to that shown in figure 2, from another case of cholecystitis.

icterus might be due to a spasm of the sphincter of the choledochus producing continual obstruction of the common bile duct, and that the spasm might be brought about by irritation within or adjacent to the gastro-intestinal tract, or even by psychic influence. Meltzer, in explaining his conception of the law of contrary innervation, considered the part the sphincter might play. Much has been written concerning this conception as applied to the gallbladder and sphincter, but few sub-

stantial data have been presented. Lyons has made a practical application of Meltzer's hypothesis in the treatment of various pathologic conditions associated with the liver, biliary tract and pancreas.

There are two possible conditions of the sphincteric mechanism of the choledochus which might be produced by pathologic conditions. These are loss of function and spasm. It is possible that disease of the gallbladder which would partially or completely destroy its con-

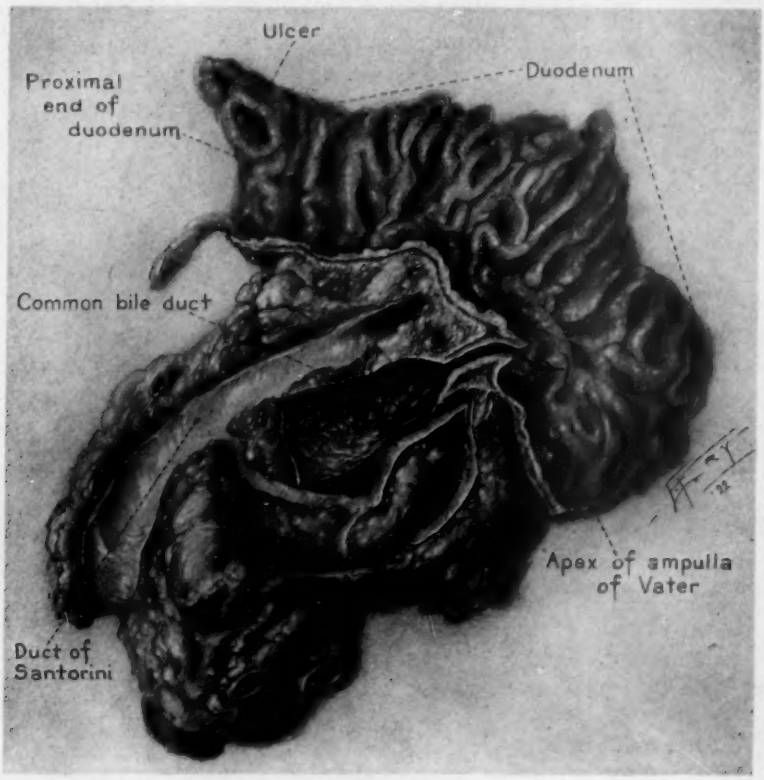

Fig. 4.—Increase in muscle around the terminal portion of the common bile duct in a case with ulcer of the duodenum.

centrating action or prevent bile from entering the gallbladder would produce the same decrease in the action of the sphinteric mechanism as often following the removal of the gallbladder. It should also be noted that some of the symptoms which follow the removal of the gallbladder may be due to a failure of readjustment between the sphincteric mechanism and dilatation of the extrahepatic biliary tract. It must also be considered that pathologic conditions, such as cholecystitis, duodenal and gastric ulcer, duodenitis, appendicitis and possibly certain

psychic disorders might reflexly produce a spasm of the sphincteric mechanism. This spasm of the sphincter would occlude both the common bile duct and the pancreatic duct in cases in which the latter enters the former. Thus the discharge of secretion from both the ducts would be prevented. If the outflow of bile were prevented long enough, or if the concentrating action of the gallbladder were impaired, jaundice might occur. If the outflow of pancreatic juice from the duct of Wirsung were prevented, various degrees of atrophy of the acinar tissue would occur in cases in which the duct of Santorini was not capable of draining the organ. If this were true, several clinical observations could be explained. A spasm of the sphincteric mechanism might be the cause of jaundice not associated with discernible obstruction of the common bile duct. Pancreatitis associated with cholecystitis might be due, in part at least, to the obstruction to the outflow of pancreatic juice.

The possible significance of the sphincteric mechanism at the duodenal end of the common bile duct in the production of obstruction to the outflow from the liver and pancreas in pathologic conditions was suggested by observations made at necropsy. It was noted that in some cases of cholecystitis or peptic ulcer, there was definite hypertrophy of the muscle bundles around the common bile duct, not only in the intramural portions of the duct but sometimes also extending a considerable distance up the duct from the duodenal wall. In some of these instances pancreatitis was also found (figs. 1, 2, 3 and 4).

SUMMARY

The physiologic and anatomic observations on the sphincteric mechanism at the duodenal end of the common bile duct are reviewed. There is definite evidence of the presence of a sphincteric mechanism at the duodenal end of the common bile duct. That this mechanism represents a true sphincter and is not simply due to variations of tone of the duodenal wall has not been definitely determined, although the former would appear to be true. The discharge of bile into the intestine is modified by and in some respects depends on peristalsis of the duodenum, but the exact relationship of the two processes is not clear. Certain specimens examined at necropsy suggest the possibility that the sphincteric mechanism can be thrown into spasm by pathologic conditions in the gastro-intestinal tract and adjacent organs. The cause of some cases of jaundice and also of pancreatitis might be explained on the basis of spasm of this sphincteric mechanism producing obstructions to the outflow from both liver and pancreas.

THE RETICULO-ENDOTHELIAL SYSTEM

III. THE INFLUENCE OF HORMONES *

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Recently, more and more attention has been paid to the function of the reticulo-endothelial cells, and it has been shown that these cells play an important rôle in the processes of defense, as well as in the intermediary metabolism of iron, fat, proteins and bile pigments.

It is still an open question whether the activities of these cells express their individual and independent function, or whether they are influenced and regulated by other factors.

In recent papers on lipoid hyperplasia of the spleen in diabetes, we have hinted at the possibility that storage of fat in certain parts of the reticulo-endothelial system might be due to hormonic influences.[1] Experimental work by Donath and Saxl [2] has also suggested that the function of the reticulo-endothelial system can be influenced by solution of pituitary. More recently, Mandelstamm [3] has shown that these cells also can be stimulated by epinephrine hydrochloride. Both papers are in accord with the observations of Louros and Sheyer,[4] who succeeded in prolonging life in animals that had streptococcic infections by administering either epinephrine hydrochloride or solution of pituitary.

EXPERIMENTS

The following experiments have been carried out in order to determine whether hormones are actually instrumental in the regulation of reticulo-endothelial function.

Trypan Blue.—A series of animals were injected with 1 cc. of a 1 per cent solution of trypan blue, every three days for three doses. A number of these animals were kept as controls, whereas the others were divided into four groups. The first group received injections of insulin; the second, epinephrine hydrochloride; the third, of solution of pituitary and the fourth, of thyroid extract. The doses given were insulin, one-third unit; epinephrine hydro-

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2. Donath and Saxl: Wien. Arch. f. inn. Med. **4**:1866, 1925.
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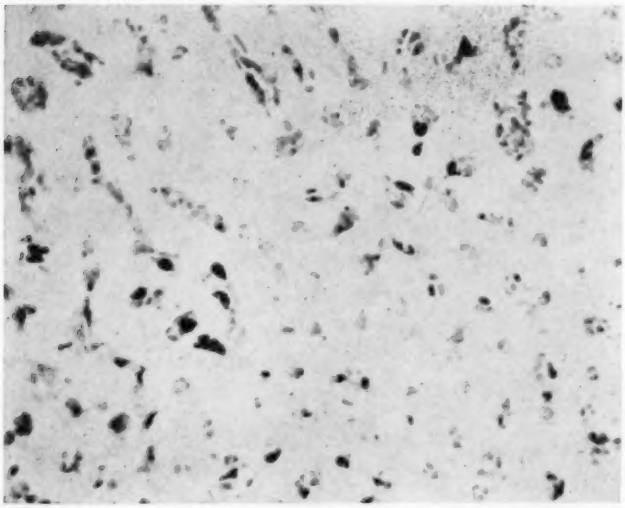

Fig. 1.—Storage of iron in the Kupffer cells of the liver in a control animal. Magnification: Leitz, apochromate 4 mm., periplane eye piece no. 6.

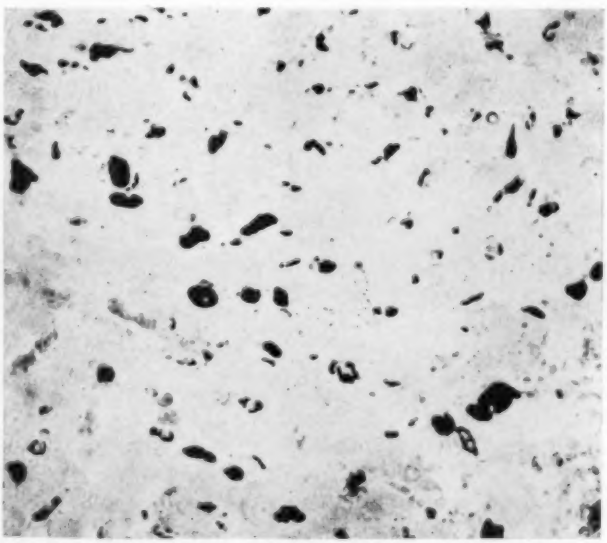

Fig. 2.—Storage of iron in the Kupffer cells of the liver in an animal given injections of solution of pituitary. Magnification: Leitz, apochromate 4 mm., periplane eye piece no. 6.

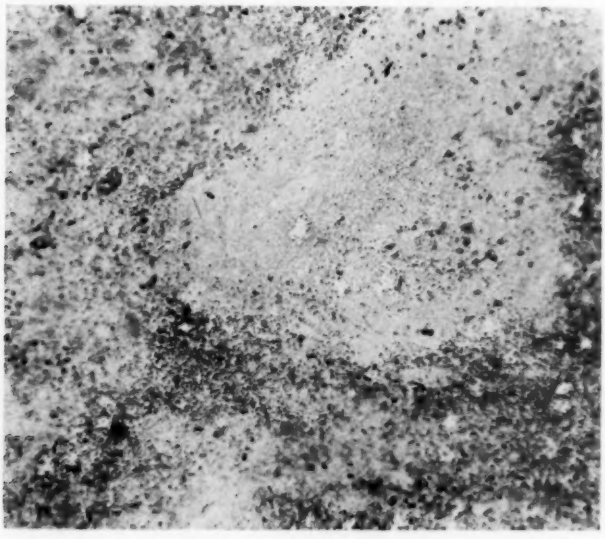

Fig. 3.—Storage of iron in pulp of spleen in a control animal. Magnification: Leitz, apochromate 16 mm., periplane eye piece no. 4.

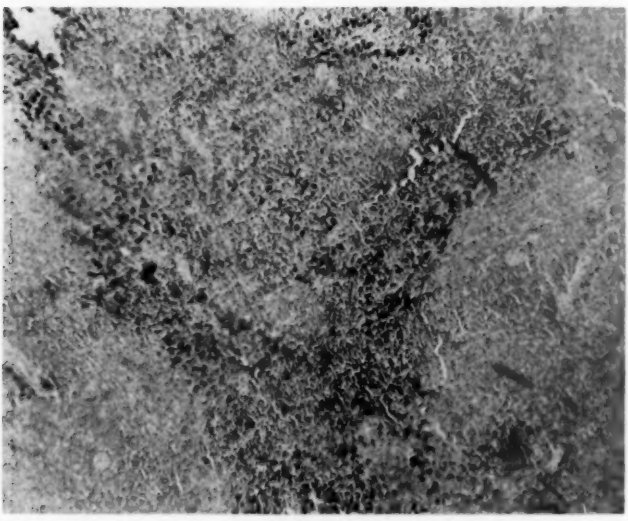

Fig. 4.—Storage of iron in pulp of spleen in animal given injections of solution of pituitary. Magnification: Leitz, apochromate 16 mm., periplane eye piece no. 4.

chloride, 0.3 cc. of 1:5,000 dilution; solution of pituitary, 0.3 cc. of 1:10 dilution of the stock solution, and thyroid, 0.2 cc. of thyroid residue. On the days on which the trypan blue was administered, three injections of the various hormones were given instead of one. Twenty-four hours after the third injection of trypan blue, all the animals were killed and their spleens and livers were preserved in solution of formaldehyde.

Microscopic examination of the paraffin sections showed that there was a good storage of trypan blue in the Kupffer cells of the liver, while the dye was much less discernible in the reticular cells of the splenic pulp. The sinus cells and the follicles of the spleen were practically free from trypan blue.

The amount of trypan blue in the Kupffer cells of the experimental animals varied considerably. It was definitely increased in the animals given insulin, practically unchanged in the series given epinephrine hydrochloride, unchanged in those given solution of pituitary, and most markedly decreased in the group given thyroid extract. The livers in the latter group contained hardly any trypan blue. The spleens were similar. The increase in the spleens of the animals given insulin was most marked, as was the almost complete absence of dye in the spleens of the animals given thyroid extract. The spleens of the animals given epinephrine hydrochloride did not show any particular changes nor were such changes observed in the series given solution of pituitary.

Iron.—One cubic centimeter of a colloidal iron solution was injected intraperitoneally into a number of animals which were again divided into five groups, one of which served as a control, while the others were treated with the four hormones, respectively, as in the experiments with trypan blue.

Twenty-four hours after the third injection of iron, the animals were killed, and again the liver and spleen were examined histologically.

Microscopically, a good storage of iron was found with both Turnbull's method and with that employing ammonium sulphide. In the liver, the Kupffer cells were loaded with fine iron granules, the distribution of which was not regular, as some of the Kupffer cells did not contain any iron while others contained varying amounts. In the spleen, the iron was stored in the reticulum cells of the pulp, and the amount of iron was particularly large in those cells which surrounded the lymph follicles, while the rest of the pulp contained much less iron. Some of the large reticular cells within the follicles were also conspicuous for their content of iron.

The group of animals given insulin did not show any change in storage of iron in the spleen, as compared with the controls. The changes in the livers were irregular, as in some cases there was a considerable increase of iron, while in others the amount was decreased. In the group given epinephrine hydrochloride, there was a definite decrease in both liver and spleen, particularly in the latter, while in the liver, the individual iron granules seemed to be somewhat coarser, although the number of cells containing iron was lessened.

In the group of animals given thyroid extract there was a considerable increase in the storage of iron in the spleen, while the amount of iron in the livers was about the same as in the group given epinephrine hydrochloride.

The largest amount of iron was found in the group given solution of pituitary, in which the spleens particularly showed excessive storage. The reticulum cells were overloaded with iron granules which surrounded the cell nucleus. The storage was most intense in the perifollicular area, but iron was stored throughout the whole pulp and in many intrafollicular reticulum cells. As to the Kupffer cells, both the number of storing cells and the amount of stored material were visibly increased.

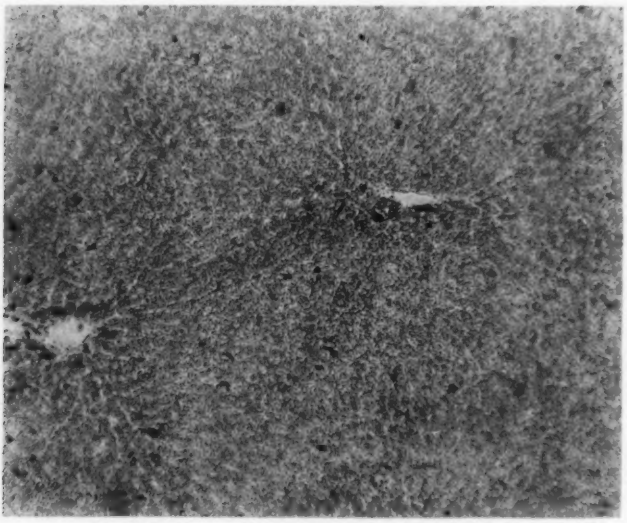

Fig. 5.—Storage of cholesterol in Kupffer cells of liver in a control animal. Magnification: Leitz, apochromate 16 mm., periplane eye piece no. 4.

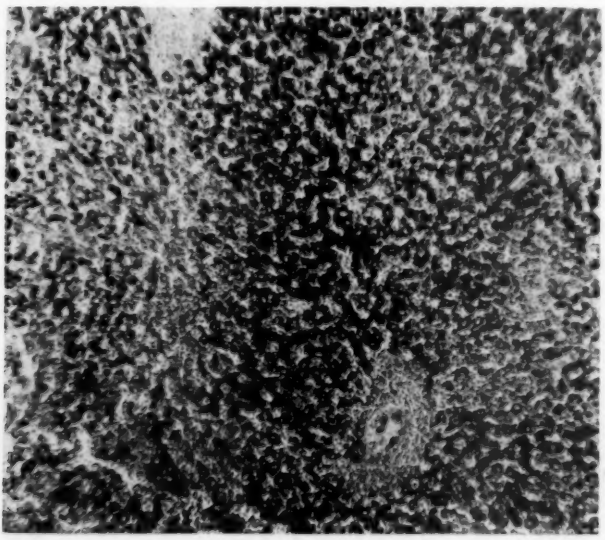

Fig. 6.—Storage of cholesterol in liver of animal given injections of insulin. Magnification: Leitz, apochromate 16 mm., periplane eye piece no. 4.

Cholesterol.—A cholesterol emulsion was used, which we obtained by dissolving a cholesterol oil mixture in absolute alcohol and emulsifying this alcoholic solution with water. The amount of cholesterol injected was calculated at 33 mg. per animal per injection. The emulsion was injected intraperitoneally. The experiment was carried out on the same plan as the two foregoing ones.

In the control animals, a fair storage of cholesterol was found in both the Kupffer cells and in the reticulum of the splenic pulp. The cholesterol was demonstrated by Sudan staining in frozen sections. The cholesterol appeared as small orange droplets within the cells of the reticulum in the spleen and in the Kupffer cells.

In the animals given insulin, an enormous increase in the storage of cholesterol was found. Most of the Kupffer cells were greatly enlarged and filled with fat droplets. Apparently, a good deal of fat was also stored in the liver cells. The increase of storage in the spleen was not so remarkable, although it was substantial as compared with the controls.

In the group given epinephrine hydrochloride, there was a slight decrease in the storage of cholesterol in the liver but not in the spleen. It seemed to us, however, that there was a slight difference in the distribution of the fat, as it appeared more conspicuously within the follicles than seen in the controls.

In the animals given solution of pituitary, there was also an increase of storage in the liver, perhaps somewhat more than in the group given epinephrine but much less than in the animals given insulin. The spleens compared well with those of normal animals, not showing any difference in storage.

In the animals given thyroid extract, few Kupffer cells showed any storage. Some of these cells contained large droplets, but the majority were free from fat. In the spleen of these animals, hardly any trace of fat could be found.

COMMENT

The results of our three experiments show that the degree of storage is markedly affected by injections of hormones, but we also observed that the effect of the hormones was different for the various materials used for storage. Furthermore, it seems that a given hormone may influence storage in the liver and in the spleen in varying degrees.

If an indifferent corpuscular material, such as trypan blue, was used as storage material, the storage was more marked in the Kupffer cells of the liver than in the spleen, and so were the changes brought about by the hormones. Insulin increased and thyroid extract decreased the storage definitely, while the changes brought about by epinephrine hydrochloride and solution of pituitary were unimportant.

In the second experiment, we stored the material that the splenic cells handle physiologically, namely, iron. Hence, it is understandable that both its storage and its variations are more marked in the spleen than in the liver. The storage in the spleen was most intense in the animals given solution of pituitary, with the series given thyroid extract second. There was no change in the group given insulin but some decrease in the group given epinephrine hydrochloride. The changes in the liver were less regular, for only in the livers of the animals given solution of pituitary and epinephrine hydrochloride, i. e., in the two

extremes, did the changes match those found in the spleen, while the livers of the animals given insulin could not be classified definitely and the changes in the livers of the animals given thyroid extract were the opposite of those in the spleens of the same series.

In the experiment with cholesterol, the changes in the livers were as striking as those of the spleens in the series given iron. The results in this experiment ran almost parallel with the experiment with trypan blue, as the greatest storage was found in the group given insulin and the least in the group given thyroid extract, while the amount of storage in the two other groups was between the two extremes.

It seems, therefore, that in the storage of trypan blue and fat—so far as the Kupffer cells are concerned—the well known physiologic antagonism of insulin and thyroid is borne out. In the storage of iron, on the other hand, the splenic reticulo-endothelial cells respond markedly to stimulation by solution of pituitary and are visibly inhibited by the action of epinephrine hydrochloride.

The difference in storage of cholesterol after the administration of insulin or thyroid extract is well in accord with the clinical observation that gain in weight, i. e., storage, may be brought about by treatment with insulin (Falta), while thyroid extract has been used for a long time in treatment for obesity.

Our first two experiments are in keeping with the conception prevailing at present of thyroid-insulin antagonism and their effect on the regulation of endocrine function. The same cannot be said about our experiments with iron. The antagonistic action of solution of pituitary and epinephrine hydrochloride on storage of iron in the spleen might still be understood in spite of the synergism that otherwise prevails in the relationship of the posterior pituitary lobe and the chromaffin tissue. It is difficult to conceive, however, that insulin should not play a part in storage of iron when we note its striking effect in the other two experiments. These same experiments have borne out the antagonism of insulin and thyroid as to their stimulating effect on the reticulo-endothelial cells, while our experiments with iron showed that both hormones are almost equally ineffective in storage of iron.

We do not want to discuss this peculiar behavior, because it would lead to mere speculation. However, it seems important to emphasize the unexpected regularity observed.

Our experiments dealt merely with one side of the problem, namely, the effect of hormones on the storage by the reticulo-endothelial system. This, however, is only one of the manifold activities of these cells, and it stands to reason that their other functions such as production of antibodies, phagocytosis, tissue immunity and metabolic activities, are also subject to similar influences. Future investigations are required to verify this assumption.

CONCLUSIONS

The storing function of the reticulo-endothelial cells can be influenced experimentally by the administration of hormones.

Storage of trypan blue or cholesterol is increased by insulin, decreased by a thyroid preparation and practically not altered by epinephrine hydrochloride or solution of pituitary.

Storage of iron is increased by solution of pituitary and partly by thyroid extract, decreased by epinephrine hydrochloride and not definitely influenced by insulin.

Hormonic stimulation of the Kupffer cells is more effective in case of the storage of trypan blue or cholesterol, while that of the splenic reticulo-endothelial cells is more effective in the storage of iron.

ANOMALOUS CONGENITAL BICUSPID SUBAORTIC VALVE OF THE HEART*

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CHICAGO

Congenital anomalies of the heart have been the subject of much investigation and speculation on the part of anatomists and embryologists. The result of these studies has been a classification of cardiac anomalies on an embryologic basis. From time to time lesions are discovered which are difficult to explain in the light of the knowledge of the embryogenesis of the heart. The potentialities of portions of the heart, more particularly the valves, for atypical development are varied and numerous, and are not fully understood. The lesion described in the following case is undoubtedly congenital and difficult to account for. It bears many similarities to a well recognized, yet infrequent, condition, namely, subaortic stenosis. Despite these resemblances it seems to be a quite different lesion and to have a different origin.

Cardiac anomalies are of importance clinically from the standpoint of differential diagnosis. This is especially true in adults, in whom the presence of atypical murmurs and thrills leads one to suspect a congenital lesion of the heart. Such was the case in this instance, but the type of lesion was not suspected, nor could it hardly have been, since the condition is certainly rare, and, as far as I have been able to determine, one not previously reported in the literature.

REPORT OF CASE

The specimen was obtained at the necropsy of Mrs. L. K., aged 40, who had been admitted to the Michael Reese Hospital in July, 1922, when a diagnosis of duodenal ulcer and mitral regurgitation was made. At that time she complained of some palpitation and precordial pain on exertion. The pain was substernal, radiating to the root of the neck and to the shoulders. The attacks were associated with blurred vision but no dyspnea. Sometimes the pain radiated to the right arm. The attacks lasted for five or ten minutes, and disappeared with rest. At the age of 14 years she was told by a physician that she had a heart murmur, but symptoms did not occur until twelve years before admission. She was then told that she had a "bad heart." There was not any history of rheumatism. On physical examination of the heart on the first admission, a palpable apical thrill was observed, and the first sound at the apex was replaced by a loud systolic murmur transmitted to the base and axilla. The pulmonic and aortic sounds were not accentuated. Both radial pulses were equal. After some time, the gastric symptoms improved, and the patient remained well until the second admission in October, 1926.

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* From the Snydacker Fund of the Michael Reese Hospital and the Nelson Morris Institute for Medical Research.

The gastric symptoms had recurred, and a diagnosis of duodenal ulcer was again made. She also complained of recurring attacks of pain radiating to the chest and back. She complained now of suffering from shortness of breath on exertion, for several years, and a moderate degree of swelling of the ankles at night. In the course of the physical examination, the heart was noted to be enlarged, chiefly to the left, with a transverse cardiac dulness of 15.5 cm. The apex beat was diffuse in the fifth interspace. A prominent thrill could be felt there. A loud, hard, systolic murmur, present all over the heart area, was loudest at the apex, and was transmitted for a short distance beyond the left border. The second pulmonic sound was accentuated over the second aortic. Except for tenderness in the epigastrium to the left of the midline, other significant physical signs were not found. Roentgenologic examination revealed a duodenal defect. The patient improved only slightly under medical treatment, and seven weeks after admission a partial gastric resection was performed. The preoperative diagnosis was "duodenal ulcer," "chronic mitral endocarditis," "cardiac hypertrophy," "slight cardiac decompensation" and "possibly a congenital cardiac lesion." The postoperative course was stormy, and five days after operation a jejunostomy was performed for what appeared to be a low grade, high intestinal obstruction. She died four days later of gastric dilatation. The necropsy revealed a dilated stomach and moderate passive congestion of the liver and kidneys.

DESCRIPTION OF HEART

The transverse diameter of the heart in situ was 14.5 cm. The right side was slightly dilated. The trabeculae of the right auricle were noticeably increased in thickness and the papillary muscles of the right ventricle were prominent. The tricuspid valve was free from thickening and the orfice measured 8 cm. in circumference. The pulmonic ring measured 4 cm., and the cusps were normal. The pulmonary artery measured 4.3 cm. in circumference 1.5 cm. above the ring. The left ventricular wall was hypertrophied, measuring 2.7 cm. in its greatest thickness; the cavity was contracted.

The main papillary muscle was greatly thickened, and tendons extended from it to an anomalous formation of the endocardium in the left ventricle, as well as to the mitral cusp (fig. 1). The aortic ring measured 4.5 cm. in circumference and before the ventricle was opened it just admitted the tip of the forefinger. The aortic cusps were thickened and shortened, the free edges were curled and the bases were firm and sclerotic, but not calcified. The muscular portion of the interventricular septum was short, so that the area occupied by the membranous portion was increased and measured 3 cm. from the base of the aortic cusps downward. The membranous portion, or the so-called undefended space, was thickened, and this thickening involved the interauricular septum where the two septums were continuous. At the lower margin of this membranous portion, the muscle wall thinned out rather abruptly. Here there was a peculiar reflection of the endocardium across the ventricle, in the form of a bicuspid valve, from the free edges of which chordae tendineae were given off. This was more marked from the cusp

nearest the mitral valve, from which well developed tendons extended to the papillary muscle mentioned previously; these crossed the tendons from the mitral valve. The chordae tendineae from the other cusp merged quickly into the posterior wall of the ventricle. The cusps were adherent to the wall of the ventricle, their inferior margins being curled upward so that they formed a slight shelf across this portion of the ventricle. The left cusp was closely attached to the aortic surface

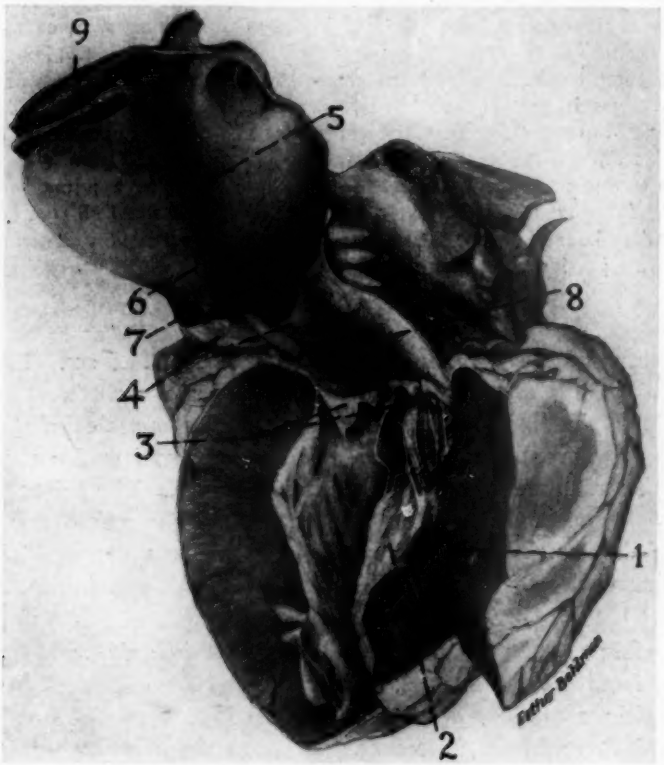

Fig. 1.—Heart opened to show the situation of the anomalous valve; 1 indicates hypertrophied wall of the left ventricle; 2, enlarged papillary muscle of the left ventricle, with chordae extending to the mesial segment of the anomalous valve and to the aortic cusp of the mitral valve; 3, the two cusps of the anomalous valve; 4, aortic valve; 5, ascending aorta; 6, misplaced ostium of the left coronary artery; 7, normally situated ostium of the right coronary artery; 8, thickened membranous interventricular septum.

of the aortic cusp of the mitral valve, being separated for about 3 mm. at its edge. The margins of this anomalous valve were slightly serrated, the bicuspid appearance being due to two well formed peaks, giving the appearance of separate leaflets. The endocardium covering the anomaly continued upward over the interventricular septum and

merged into the root of the aorta. It was thickened and slightly irregular. Grossly, the whole valve might have been described as sclerotic. The position of this valve must have offered some resistance to the free flow of blood from the ventricle. The mitral valve was free from thickening, except at the line of closure. A few irregular, yellow patches were present at the base of the cusps. The mouth of the left coronary artery was displaced upward, and was situated 2 cm. above the free border of the posterior aortic cusps. The root of the aorta was elastic and smooth. The arch measured 7 cm. in circumference, just before

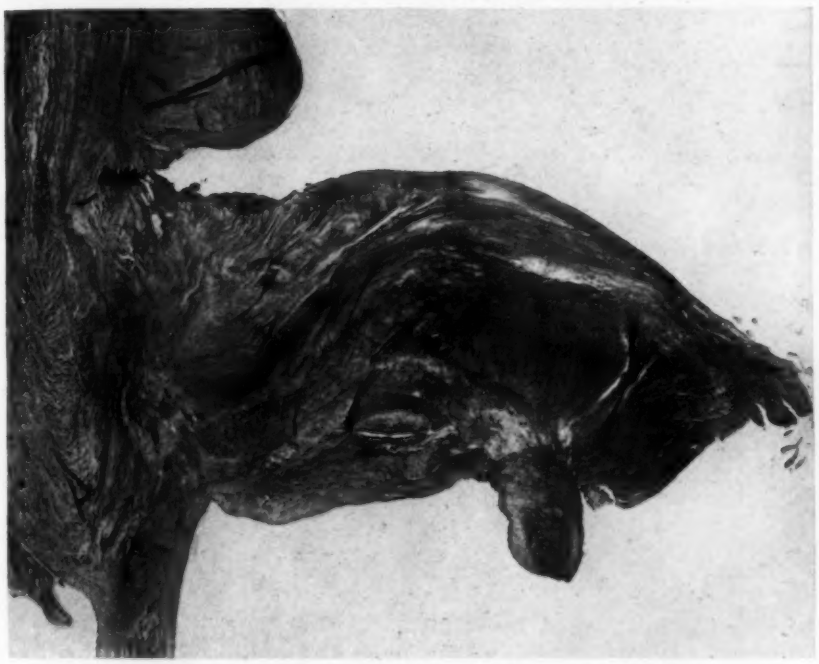

Fig. 2.—Section through the mesial cusp of the anomalous valve; × 17; at the right the tip of valve with attachment of chorda; at the left below the thin muscular portion of the interventricular septum; at the left above the thickened membraneous portion of interventricular septum.

the great vessels were given off. Immediately beyond this point there was a marked narrowing of the descending arch which measured only 4 cm. in circumference. This portion widened out into the thoracic aorta, where the circumference was 4.5 cm. The intima was smooth and yellow, presenting a few raised, yellow plaques, situated at the beginning of the narrow portion, and at the mouths of the abdominal vessels. Dimpling of the intima was also noticeable at the beginning of the narrowed arch.

MICROSCOPIC EXAMINATION

Microscopic sections of the values and various portions of the aorta were stained by Mayer's acid hemalum and eosin, by van Gieson's stain and Weigert's iron hematoxylin to demonstrate connective tissue and smooth muscle and by Weigert's and Unna's methods for elastic tissue. The anomalous valve (fig. 2) was covered by hyaline connective tissue. The endothelium was present in a few areas, but was mostly hyalinized

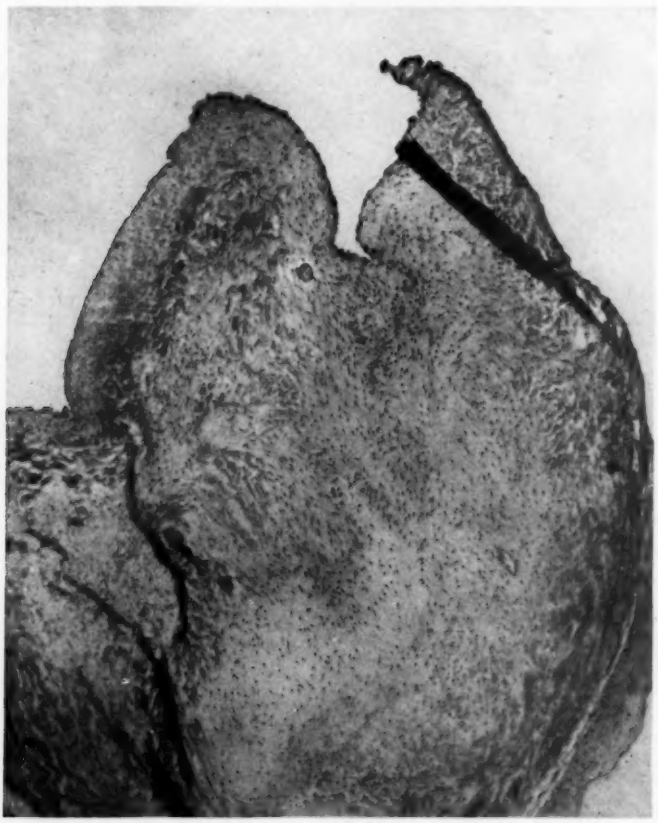

Fig. 3.—Mesial cusp of anomalous valve; Mayer's acid hemalum and eosin; ×48; the tissue is somewhat more cellular than in the lateral cusp.

and merged into the connective tissue. A small amount of fatty change had taken place, especially about the base, where the sclerosis was more marked. The free portion and edge of the valve was represented by a bulbous swelling formed by connective tissue cells, separated by a faintly staining ground substance. The transition into the ventricular endocardium could be made out. The latter also showed some hyaline thickening. The tissue between the free borders of the valves and the

aortic cusp was thickened and fibrous, and the aortic cusps were sclerotic. A section through the cusp adherent to the mitral valve showed a slighter degree of sclerotic thickening in the mitral cusp with about the same degree of sclerosis and hyaline change in the anomalous cusp, but the thickening in the anomalous valve was due to moderately cellular connective tissue (fig. 3). The condition was one of chronic sclerosing endocarditis. A few coarse strands of elastic tissue were present in the valve, especially about the base. Sections of the aorta were studied with a view to explain the localized narrowing. Except for the areas of intimal sclerosis in which slight calcification had occurred, pathologic changes were not found. The amount of elastic tissue was not appreciably different in this narrow portion than it was in other sections.

COMMENT

A search was made in the literature for a description of a similar lesion, but none was found. Dr. Maude Abbott, in a personal communication, stated that she had never seen such a specimen. It seems possible to account for this anomaly only on a congenital basis, but it is difficult to explain how it might have occurred. The lesion which it most nearly resembles is subaortic stenosis, of which Maude Abbott [1] writes:

> Subaortic stenosis is an annular thickening of the endocardium of the left ventricle, generally a few mm. below the aortic valves. It involves the base of the aortic segment of the mitral valve, encircles the ventricular wall at this point, and leads in most of the cases to a localized narrowing of the cavity. The thickened ring of tissue is often the seat of a chronic inflammatory process, probably of later incidence, but there can be little doubt that it is at least in a certain proportion of cases of congenital origin. Keith explains it as an arrest of development analogous to the conus stenosis of the right ventricle, the bulbus failing to atrophy about the root of the aorta. It does not necessarily interfere to any serious extent with the passage of blood into the aorta. Therefore, the clinical picture differs from that of a valvular stenosis at the aortic orifice by the absence of the usual symptoms of a diminished circulatory output in the presence of a highly characteristic long, drawn out, harsh systolic murmur with a maximum intensity in the third right interspace, but transmitted widely over the whole chest and into the vessels of the neck, and accompanied in most cases by a systolic thrill. The subjects are generally strong, vigorous young adults, who have shown no pallor or tendency to fainting or the slow, small pulse significant of an aortic obstruction.

This description of subaortic stenosis offers a few similarities to the lesion and history in this case. Clinically the condition here recorded differs in the position of maximum intensity of the murmur, and patho-

1. Abbott, Maude E.: Congenital Diseases of the Heart, in Osler and McCrae: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1926, vol. 4, pp. 612-812.

logically it differs in the lower position of the transverse band, the shape of the band and its attachment to the wall of the ventricle by true tendons.

The position of this anomaly leads to a consideration of the embryology of this portion of the heart and root of the aorta. This portion of the heart develops out of the embryologic structure known as the bulbus cordis, and quoting again from Abbott's monograph:

> The bulbus cordis is a name given to a transitory portion of the embryonic heart, leading from the right end of the common ventricle to the aortic arches. In the human embryo of from 4 to 6 mm. in length the bulbus is a thick-walled muscular tube passing to the left and upward, lined like the rest of the heart with endothelium, which presents certain endocardial thickenings, spirally arranged, the so-called proximal and distal bulbar swellings, structures which later form the anlagen of the semilunar cusps as well as of the lower part of the aortopulmonary septum. In later stages the bulbus disappears, its proximal portion undergoing obliteration on the side of the left ventricle, becoming incorporated on the right side in the musculature of the expanded infundibulum and body of the right ventricle, and its distal part, denuded of its musculature and considerably elongated, constituting the primitive aortic trunk. The researches of Greil on reptiles and Keith on the human heart, and of Robertson on the fish show that the mammallian bulbus represents what was at one time an independent chamber with muscular walls and its own system of multiple valves which in the ontogenetic telescoping of phylogenetic stages has become submerged.

Possibly the anomalous valve in my specimen resulted from incomplete regression or obliteration of the valvular system of the bulbus cordis, despite the fact that the aortic cusps are well formed. The anomaly thus resulting from the incomplete atrophy later became thickened by a chronic inflammatory process, which extended into the endocardium covering the interventricular septum, causing this, too, to become thickened and sclerotic.

However, the absence of any anomaly in the formation of the root of the aorta casts some reasonable doubt on the plausibility of this genesis of the condition present. The striking bicuspid formation of the anomaly immediately suggests its resemblance to the mitral valve and another possibility for its origin, namely, an anomalous formation of the auriculoventricular valve of the left side. The type of anomaly would be determined by the period in which the change or arrest in development occurred. If this particular anomaly had resulted from a double formation of the mitral valve one would expect to find other congenital defects, more especially of the septums, as in those cases reported of double mitral ostia, since such a reduplication would most likely have formed from a splitting of the primary endocardial cushions. On the other hand, this anomaly might be traced to a malformation in a later stage in the embryologic development and account for its singularity. Thus, it might be explained by a separation of the two endocardial

layers forming the cusps at the time of their invasion of and fusion to the ventricle wall. In this process, the endocardium is undermined or, in other words, the valves are split, to allow for the change from a simple endocardial fold to a tendinous structure. The ventricular surface of the valve might have been sufficiently separated to allow it to hang free and thus by a process of involution, became attached to the posterior ventricular wall, yet maintained its attachment to the papillary muscle. This would then explain the presence of a normally developed and functioning mitral valve.

SUMMARY

An anomalous bicuspid valve in the left ventricle is described. In position it resembled a subaortic stenosis. Clinically, it gave rise to a loud systolic murmur and thrill most prominent at the apex. It caused some obstruction to the outflow of blood, leading to hypertrophy of the left ventricle. In structure it closely resembled the mitral valve. The possible embryogenetic origins of the lesion are discussed. In addition to this anomaly there was a misplacement of the ostium of the left coronary artery and a localized hypoplasia or coarctation of the arch of the aorta.

ORIGIN OF PULMONARY PLUGS IN SUPRARENALECTOMIZED RATS *

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AND
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Recently Scott and Thatcher [1] reported plugs of mononuclear cells in the vessels of the lungs of double suprarenalectomized rats into which 50 per cent egg albumin in physiologic sodium chloride solution had been injected. These plugs were not found in rats with one suprarenal intact which had been similarly treated and killed a few hours after the injection. It was proved by the use of special stains that these plugs were not thrombi. This work has been repeated in order to investigate the type and origin of cells forming the plugs.

METHODS

The experiments were performed on fifty-five rats (*Mus norvegicus-albinus*) which were kept in separate cages before and after operation and which were treated in the same manner as the Scott and Thatcher series. Rats in which at least a part of one suprarenal remained were used as controls. Injections were made within from thirteen to eighteen days after the operation into all rats that survived. This was considered sufficient time, because trauma would be eliminated as a factor causing death, because the likelihood of plugs was reduced after the fourteenth day, and because usually plugs were not present after the twenty-first day.

Both albumin and india ink were injected—the albumin to kill the rat and the ink as a test agent for the phagocytic property of the cells. A fresh bottle of ink was filtered and then diluted, in the proportion of 1:10, in physiologic sodium chloride solution. One cubic centimeter of diluted ink and 1 cc. of egg albumin were mixed and injected into the femoral vein. In a few rats, a slight amount of the mixture did not enter the vein.

India ink was used because, according to Foot, carbon is taken up only by cells originating in the capillary endothelium and in the liver, and is probably not phagocytosed by cells outside of the vessels. McJunkin [2] claims that the ingestion of carbon is limited to the mononuclear cells

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* From the Departments of Pathology and Microscopic Anatomy, University of Arkansas School of Medicine.

1. Scott, W. J. M., and Thatcher, H. S.: Pulmonary Emboli in Suprarenal Insufficiency, Arch. Path. & Lab. Med. **2**:806 (Dec.) 1926.

2. McJunkin, F. A.: Am. J. Anat. **25**:27, 1919.

of the blood and to the endothelium of the capillaries. Brickner,[3] as a result of the study of the distribution of injected ink in the tissues of the rabbit, concluded that the pulmonary endothelium is not especially avid for carbon, not as avid as Kupffer cells and no more than the monocytes of the blood. He stated that colloidal carbon is ingested by cells other than endothelium and cannot be used as a test agent for the origin of these cells. His work does not invalidate colloidal carbon for our purpose, as we used it only to test the property of phagocytosis in the cells of the plugs.

The rats with both suprarenals removed died after injection, and control rats were killed within from a few hours to twenty-four hours after injection. In nine doubly suprarenalectomized rats the spleens were also removed in order to eliminate that organ as a factor in the production of the cells of the plugs. Complete autopsies were performed, and the viscera and the brain were examined grossly and microscopically. Numerous sections were made of the lungs, liver, intestinal tract, bone marrow and accessory suprarenals.

RESULTS

Only thirty-two rats are included, because operative trauma, infections and other causes eliminated the other twenty-three. Thirteen rats were doubly suprarenalectomized; they were treated with egg albumin, and the lungs were examined. Plugs were present in all except two. Seven rats died before injection, presumably from suprarenal insufficiency. Plugs were found in six. Twelve rats served as controls; plugs were found in only one of these. In this rat there was only a small piece of the right suprarenal gland.

Carbon was present in the plugs in all of the rats injected with ink except one. Some of the plugs were in the process of formation (fig. 1), clearly demonstrating the cells budding from the wall of the blood vessel and one cell almost broken off from the lining endothelium. Mitotic figures could not be found in any of the plugs. Foot[4] stated that mitotic figures are difficult to find. Permar[5] added that the absence of mitotic figures does not necessarily mean that the endothelium is inactive. None of the mononuclear cells were seen in the tissues outside of the blood vessels. The time might have been too short.

We have decided to call these cells endothelial phagocytes, which is in agreement with Foot.[4] They originate from the endothelium and have the power of phagocytosis; hence they are endothelial phagocytes.

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3. Brickner, R. M.: Bull. Johns Hopkins Hosp. **40**:90, 1927.
4. Foot, N. C.: J. Exper. Med. **33**:271, 1921; ibid. **34**:625, 1921; ibid. **37**: 139, 1923; Anat. Record **30**:15, 1925.
5. Permar, H. H.: J. M. Research **42**:147, 1920; ibid. **44**:27, 1923.

Smith [6] showed that the power of ingesting melanin is shared by such a wide variety of cells that he questions whether the faculty of melanin ingestion makes a cell a phagocyte. The ability to ingest carbon is as yet an unquestioned test for phagocytosis. These cells are not lymphocytes, because, according to Nagao,[7] the latter only rarely ingest carbon. The oxydase stain was not used in this differentiation, because it was not applicable to the blood of the rat (Doan and Sabin [8]). There is no other method to be used with this material which would determine whether the cells are monocytes or clasmatocytes. Intra vitam staining requires at least twenty-four hours (McJunkin), and the time interval in this series was from two to three hours. Long and narrow cells, such

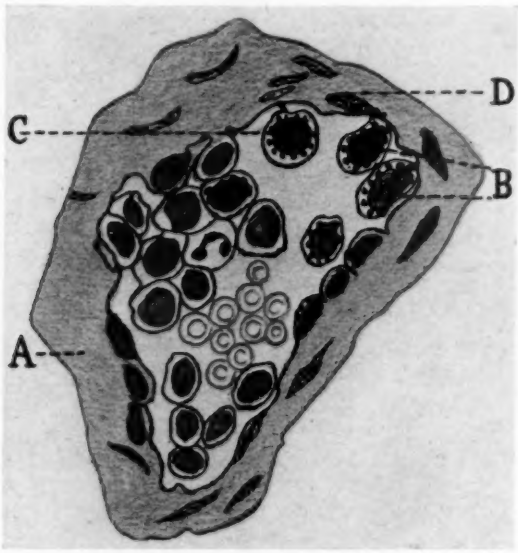

Fig. 1.—Blood vessel of lung containing partially formed plug (oil immersion objective and no. 5 ocular were used). *A* indicates the wall of the blood vessel of the lung; *B*, cells budding from the endothelial lining and containing carbon particles; *C*, cell breaking from the endothelial lining; *D*, endothelial cell of the blood vessel containing carbon.

as Sabin and Doan [9] described, were not found. They demonstrated these cells to be desquamated endothelial cells and gave them the name of endothelial phagocytes.

In the formation of the plugs, endothelial phagocytes are active. It is not a certainty that all of the cells of the plugs belong to this type.

6. Smith, D. T.: Bull. Johns Hopkins Hosp. **32**:240, 1921.
7. Nagao, K.: J. Infect. Dis. **27**:527, 1920.
8. Doan, C. A., and Sabin, F. R.: J. Exper. Med. **43**:839, 1926.
9. Sabin, F. R., and Doan, C. A.: J. Exper. Med. **43**:823, 1926.

It cannot be proved that endothelium of the lung is the exclusive source of the origin of these phagocytes, as not all cells showed ingested carbon. The plugs were produced in two examples in which the spleen had been removed, proving that organ unnecessary for their production. Signs of abnormal activity were not seen in the lymphatic tissues, spleen or bone marrow of other rats. A relation between Kupffer cells and these plugs could not be demonstrated by careful study of the liver.

COMMENT

We realize the necessity of caution in stating that the source of the cells is in the endothelium of the lung vessels. Lewis,[10] in work on living frogs, concluded that phagocytic cells accumulating in the lungs following the introduction of carbon came from the leukocytes of the blood, and not from the endothelium of the lung. Westhues [11] doubted the ability of lung endothelium to bud off cells, because he saw no signs of activity there. Wislocki [12] identified cells appearing in the lung in response to intravenous injection of particulate matter and proved them to be clasmatocytes, but he could not find any evidence of their origin. Evans [13] stated that it is possible to produce macrophages in other than the specific endothelia. Herzog [14] reported observations on the living frog's tongue. In the vessels of the tongue he saw endothelial cells budding off, breaking loose to circulate in the blood stream, and later migrating through the wall into the tissues. The migration took place at least a day after breaking loose from the endothelium, which might explain why we did not see any cells in the tissues. Permar demonstrated phagocytes budding from the endothelium of the capillaries surrounding the alveoli of the lung, and later migrating into the lumina of the alveoli. Foot also observed this origin for endothelial phagocytes. Our endothelial buds correspond to the work of Herzog, Permar and Foot; but, as stated by Permar, we cannot rule out the extrapulmonary sources of these cells.

Criticism might be offered that the plugs may represent a filtering out of macrophages produced in showers with the injection of india ink, as described by Simpson.[15] Foot also demonstrated that colloidal carbon was removed principally by the lungs after splenectomy. In either case we might get pictures resembling the plugs of our series, but as a result of the injection of the ink. Plugs were obtained, however, in six rats that died before they were given injections of ink. Ink was injected in like manner into the control rats, and they were killed at intervals

10. Lewis, M. R.: Bull. Johns Hopkins Hosp. **36**:361, 1925.
11. Westhues, H.: Beitr. z. Path. Anat. u. z. allg. Pathol. **70**:223, 1922.
12. Wislocki, G. B.: Am. J. Anat. **32**:423, 1924.
13. Evans, H. M.: Am. J. Physiol. **37**:243, 1915.
14. Herzog, Fritz: Klin. Wchnschr. **3**:535, 1924.

approximating those in which the doubly suprarenalectomized rats died after injection. These controls did not contain any plugs in the vessels of the lungs.

Plugs are present in the capillaries of the lungs of suprarenalectomized rats in this series and in that reported by Scott and Thatcher. The fact that endothelial phagocytes are found in these plugs demonstrates a relation to the reticulo-endothelial system. This phenomenon may illustrate a relationship between between the function of the suprarenal cortex and anaphylactoid shock, because pathologic changes in the gastro-intestinal tract are similar. This is a separate problem and would require further investigation.

SUMMARY AND CONCLUSIONS

1. Rats which are doubly suprarenalectomized and which receive injections of albumin and india ink from thirteen to eighteen days after operation develop plugs in the blood vessels of the lungs.

2. Control rats with one suprarenal, similarly treated, do not have characteristic plugs. When only a portion of the suprarenal is intact, plugs are not usually produced.

3. Plugs are present in six out of seven doubly suprarenalectomized rats dying in the interval before injection.

4. Endothelial phagocytes are active in the formation of these plugs.

5. Some of the endothelial phagocytes of these plugs originate from the endothelial lining of blood vessels of the lungs.

Laboratory Methods and Technical Notes

THE CARBON DISULPHIDE-PARAFFIN METHOD OF EMBEDDING TISSUES AND THEIR SUBSEQUENT HANDLING AND STAINING BY HEMATOXYLIN AND EOSIN*

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The new method of embedding tissues in paraffin that I shall describe is not ideal, but perfection can hardly be claimed by those who champion the many other methods. The method as described is not original, but is a slight modification of that described by Wood. Wood has informed me that he has used the original method in his laboratory for a great many years with complete satisfaction.

One of the strong objections to embedding tissues in paraffin is the shrinkage and other undesirable artefacts that result from the alcohols used in dehydration and from the paraffin solvents (xylene, chloroform, etc.) used to prepare the tissue for the paraffin infiltration. Another valid objection, which is perhaps the crowning abuse, is exposure of the tissue to prolonged high temperature in the paraffin oven. Considering the treatment accorded tissues in the procedures demanded by many methods and practiced in many laboratories, it is not surprising that many sections show extreme distortion; this makes it decidedly difficult to interpret pathologic changes accurately.

This method has the drawback of being somewhat slower than most others used, and the odor and inflammable character of the carbon disulphide might be charged against it. After considerable experience in using it, it would be unfair to maintain its infallibility as far as nondistortion of the tissues is concerned, but it is my opinion that if this method is carefully followed it yields tissues from which sections can be secured with the pathologic changes more faithfully preserved than is possible by the other procedures I have tried.

METHOD

When I was trying different agents to find what would give the desired dehydration without undue shrinkage, Prince, of the Army Medical Museum, suggested that *n*-propyl alcohol might be used as a substitute for absolute alcohol in the final stage of dehydration. I tried this, and the results have been satisfactory after more than a year.

Fixation of specimens may be carried out as desired. After fixation in 10 per cent formalin and selection of the blocks, it is desirable to wash the tissues in running water for from one to several hours if time permits. Although this is not imperative, tissues appear to stain with better differentiation if they are washed.

The tissues are then run through the following solutions:

1. Eighty per cent alcohol at room temperature, from four to six hours.
2. Ninety-five per cent alcohol at room temperature, from four to six hours.

*From the Division of Experimental Surgery and Pathology, The Mayo Foundation.

3. First *n*-propyl alcohol at room temperature, from six to eight hours.

4. Second *n*-propyl alcohol at room temperature, from six to eight hours.

5. Carbon disulphide and propyl alcohol (equal parts), from six hours to over night.

6. Carbon disulphide, from six hours to over night. (The material usually becomes translucent and sinks to the bottom of the bottle.)

7. Carbon disulphide and 20 per cent paraffin, from six hours to over night.

8. Carbon disulphide and 68 per cent paraffin in the 37 degree incubator, from six hours to over night.

The tissue is introduced into the melted paraffin and is allowed to remain in the oven for two hours at a temperature not exceeding 55 C. It is advisable to leave the tissue in the solution of carbon disulphide and 68 per cent paraffin over night, so that the material can be placed in the oven in the morning.

The tissue is then placed in a paper box on which the number of the specimen is recorded. Melted paraffin, no hotter than necessary, is poured around the specimen. The embedded material is placed at once in the refrigerator to prevent crystallization of the paraffin. The block is usually ready for sectioning in one hour.

The time given for steps 1 to 6, inclusive, may be extended to suit the convenience of the individual worker without danger of distorting the tissue. When haste is not particularly important, the tissues may be moved to the succeeding solutions at 8 in the morning and again at 5 in the evening. In steps 7 and 8, the procedure already defined should be rigidly adhered to. If for diagnostic reasons it is desirable to rush the process, small blocks, from 0.4 to 0.5 cm. square, should be selected. They should be left in the various solutions (except 8) for one or one and a half hours in the 37 degree incubator. By this means, fixed material obtained by 8 one morning can be embedded and ready for sectioning by 10 the next morning. The temperature of the incubator causes the solutions to infiltrate the tissues much faster than when they are at room temperature.

Complete dehydration is imperative; if 50 cc. of alcohol solution is used in steps 1, 2 and 3, it is well to discard it after from twelve to fifteen tissues of ordinary size are passed through it. If a greater volume of alcohol is used, more blocks can be passed through in proportion before it is necessary to change the fluids. It is necessary to discard the second propyl alcohol only after fifty or sixty tissues have passed through it.

The paraffin used with the carbon disulphide and in the paraffin oven is the ordinary parowax obtainable at any grocery store. That used in the oven is mixed with 5 per cent of white beeswax. The paraffin and beeswax should be melted separately before being poured together, as this effects a better mixture. The paraffin to be used around the specimen in the box is harder, with a melting point of 56 C. It should also contain 5 per cent of white beeswax. The addition of the beeswax is particularly desirable, since it renders the paraffin less fragile and more waxy. This tenacity is especially valuable when serial sections are to be made.

It is not necessary to use the highly refined paraffin for infiltration, the cheaper household product being perfectly satisfactory. All paraffin used should be melted and filtered through paper (in the paraffin oven) to remove any debris that might damage the knife of the microtome.

The blowing out of corks from the pressure exerted by the volatilized carbon disulphide in the various bottles can be avoided by the simple expedient of cutting a V-shaped longitudinal slit in the surface of the cork through which

the evaporated gas can escape as it is formed. Such corks should be provided for the bottles in steps 5, 6 and 7.

One should learn to depend less on the thermometer and more on the melting point of the paraffin within the oven in regulating the temperature of the paraffin oven, which should not be any higher than is necessary to liquefy the paraffin. A proper temperature is reached when the paraffin within the oven is covered by a thin film of unmelted wax. If one regards this criterion, the danger from overheating is considerably reduced.

In this procedure, the length of time the tissues must remain in the paraffin oven is reduced to two hours because of the preliminary infiltration with paraffin solutions in steps 6 and 7. Especially important is step 7, in which the tissues are in a solution of 68 per cent paraffin at a temperature sufficiently high to keep the mixture liquid, yet low enough to obviate the possibility of injuring the tissue by excessive heat. In fact, most of the infiltration occurs in this paraffin solution which is kept at 37 degrees and as a consequence the tissues need to be kept at the higher temperature for a relatively short time to complete the process of infiltration.

PREPARING THE SECTIONS FOR STAINING

For best results the paraffin blocks should be left in the icebox until just before sectioning. If the blocks are too cold, the temperature of the room soon renders them sufficiently warm for proper manipulation. The blocks should be trimmed and fastened to wooden blocks or to object-holders for sectioning. If ribbons are desirable, as they are in this method, a liberal matrix of paraffin must be left on the two sides of the block which parallel the edge of the knife of the microtome.

The first essential to satisfactory sections is a sharp knife; it is here that time, experience and patience are necessary in order to achieve the best results. The knife can usually be kept in proper condition by proper stropping and somewhat less honing. A knife is not in good condition unless the edge is perfectly smooth when viewed under the microscope.

As the sections are obtained, they may be affixed to the slide by the use of Meyer's albumin solution or, preferably, by the method described by Whitman,[1] which is as follows: As the sections ribbon off the block, they are transferred with forceps and a moistened camel's-hair brush to a rectangular, gray-enameled pan containing a solution of egg-white which should be kept at a temperature of 44 C. As the ribbon of sections is lowered to the surface of the fluid in the pan, it should be gently stretched to remove as many of the wrinkles as possible. Usually, several minutes are consumed in obtaining perfectly flat sections. They are cut apart with a hot spatula or scalpel and mounted by dipping the slide in the solution and bringing it up under the sections desired. The slides are then transferred on edge to the staining-rack and placed in the 37 degree incubator for from two hours (in case of haste) to over night (as a routine). The number of the tissue should be scratched on the respective slides with a glazier's point. This instrument is superior to the wax pencil in that the resulting identification number is indelible, and the confusion caused by slides losing their numbers during the staining process is avoided.

The solution of egg-white is made as follows: The white of one egg is beaten into from 75 to 100 cc. of water. The mixture is filtered for twenty-

1. Whitman, R. C.: Some Time-Saving Devices for Handling Paraffin Imbedded Material, J. Lab. & Clin. Med. **7**:240, 1922.

four hours, and if it all passes through the filter paper, 4,000 cc. of water is added. If all the egg-white does not pass through the filter, less water in proportion is added. A crystal or two of thymol should be added as a preservative. The portion of the solution used should be filtered from time to time and more thymol added as necessary. When not in use, the solution should be kept in a corked receptacle to avoid evaporation and contamination with dust.

The slides must be scrupulously clean; otherwise, difficulty may be experienced in making the sections adhere during the process of staining. Clean slides are available if a supply is kept in the following solution recommended by Mallory and Wright.[2]

Bichromate of potassium	8 Gm.
Sulphuric acid	12 cc.
Water	100 cc.

A half liter of this mixture should be kept in an ordinary quart fruit jar, which is large enough to accommodate a hundred or more slides. From this solution the slides are transferred to running water and then to 95 per cent alcohol, after which they are wiped and put away in dust-proof containers until needed. With slides cleaned by this method, no difficulty is experienced from sections loosening. When sections fail to adhere to the slides, it is due in practically every instance to improper cleansing.

This method of handling sections is quicker and neater than using an albumin-glycerin fixative on each slide and placing the individual section thereon. After one has become familiar with this technic, one appreciates its many advantages. It has a distinct value in preparing slides for a collection to be used in teaching in which many sections from the same block are necessary, and in obtaining serial sections for research study. It also fills with perfect satisfaction the demands of the diagnostic laboratory, in which good sections properly stained are always desirable but not always obtained.

STAINING

Sections are removed from the 37 degree incubator and passed through the following steps:

1. Xylene, two minutes.
2. First absolute alcohol, two minutes.
3. Second absolute alcohol, one minute.
4. Eighty per cent alcohol, two minutes.
5. Thorough washing in running water until all evidence of xylene and alcohol has disappeared and water adheres evenly over the entire slide. (If the slides are to be handled in racks, they should never be placed back to back in direct apposition; there should be a space between each slide to enable fluids to circulate.)
6. Delafield's[3] hematoxylin, from seven to ten minutes (seven minutes is usually sufficient).
7. Thorough washing in water.
8. Decoloration in acid alcohol by raising and lowering the rack of slides to the rapid count of fifteen.

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2. Mallory, F. B., and Wright, J. H.: Pathological Technic, ed. 8, Philadelphia, W. B. Saunders Company, 1924, pp. 666.

3. Delafield, Francis; and Prudden, T. M.: Textbook of Pathology, ed 13, New York, William Wood and Company, 1925, pp. 1354.

9. Thorough washing in water.

10. Treatment with dilute ammonium hydroxide solution, until the sections turn blue, from one to several minutes. (This solution is made by adding a drop or two of weak ammonia solution to the tray of water.)

11. Thorough washing. (All traces of the ammonium hydroxide must be removed if a proper eosin stain is to be obtained.)

12. Treatment with 1 per cent potassium alum solution, from two to four minutes.

13. Rapid immersion in water, the slides being allowed to remain for about one second. (Care should be taken to avoid too much washing, as the alum will be lost.)

14. Treatment with 1 per cent of a saturated aqueous bluish solution of eosin, one minute, timed accurately by the watch.

15. Thorough washing in water.

16. Eighty per cent alcohol, from a half to one minute.

17. Ninety-five per cent alcohol, from a half to one minute.

18. Beechwood creosote, from five to ten minutes (for the purpose of clearing).

This is a good method of staining which may be used as a routine, especially for tissues that have been fixed in formalin. This technic may be modified to give good results with tissues fixed in Zenker's solution. They should be placed in compound solution of iodine (Lugol's solution) for fifteen minutes before being treated with hematoxylin (after step 4) to remove the precipitated mercuric oxide crystals. This should be followed by momentary immersion in a 5 per cent solution of sodium thiosulphate ("hypo") to remove the iodine.

Occasionally, after fixation in formalin, certain tissues, particularly those of the common fowl, fail to take an eosin stain satisfactorily. The use of the 1 per cent potassium alum solution in step 12 has precluded this difficulty; the alum, which is deposited as aluminum hydroxide, acts as a mordant that reacts with the eosin to form a stable compound. As a consequence of using this agent, all sections take a uniform eosin stain that adds materially to the differentiation usually expected from the hematoxylin and eosin combination.

MOUNTING

After the slides have drained for several minutes, they should be wiped carefully with a cloth moistened in xylene or 95 per cent alcohol and as much of the creosote removed as possible. Care should be taken not to approach too near the section, since it may be badly damaged if touched during wiping. The slides should be placed, with the section up, on paper toweling or blotting paper, and blotted with a clean piece of blotting paper. Gentle pressure should be used to remove the creosote. A small drop of thin Canada balsam should be placed in the center of each section and a cover slip placed thereon. The balsam must not be too thick; it can be kept at the right consistency by the occasional addition of a small amount of xylene. An overabundance of balsam should not be used in mounting sections, since it takes longer to harden and there is danger of getting a smeary preparation.

To prevent any decoloration of the mounted sections from acidity that may develop or be present in the balsam, anhydrous calcium carbonate in excess may be added to the balsam. The mixture is shaken vigorously and then is allowed to stand several hours, after which it is filtered in the 37 degree incubator.

General Review

THE QUANTITATIVE RELATION OF SERUM ALBUMIN AND GLOBULIN *

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Examination of the blood and of its various constituents has always held an important place in the investigation of disease, with attention focused largely on the formed and nonprotein elements. Significant changes also occur in the serum proteins, as has been shown by numerous determinations since the middle of the last century. Credit for the earliest measurements belongs to Becquerel and Rodier (1844), and it is interesting to note how closely their calculation of 7.6 per cent protein agrees with subsequent work. Since that time, a number of different methods have been devised for the quantitative determination of the serum proteins, the publication of each new method being followed by renewed interest in the subject. With progress from the older cumbersome procedures to the modern more rapid and simple methods, variations in the serum proteins have become significant in the diagnosis and prognosis of many pathologic processes, and in the comprehension of their general nature.

The earlier gravimetric and chemical methods involved the precipitation of the protein or of its fractions, and required a relatively large amount of serum. Either the precipitate was washed, dried and weighed directly, or its nitrogen content was determined by the Kjeldahl method, and multiplied by the factor 6.25 to convert it into protein. As precipitants, tenfold dilution of the serum, acetic or carbonic acid, alcohol and various salts have been used, the latter most frequently since different concentrations can be used to separate the protein fractions.

Hammarsten in 1878 described the method of precipitating the globulin by saturating the serum with magnesium sulphate, collecting, drying and weighing the precipitate. In human serum he found an average of 7.6199 per cent protein, 4.516 per cent albumin and 3.103 per cent globulin. The average ratio of globulin to albumin was 1 to 1.511. Nearly ten years later, Kauder showed that globulin was completely precipitated by half saturated ammonium sulphate, while albumin was precipitated only by the fully saturated salt. Pohl adapted this method to the quantitative determination of serum globulin. Halliburton (1884) used magnesium sulphate to separate fibrinogen, and precipitated

* Aided by a grant from the Fenger Memorial Association.

globulin with sodium nitrate, acetate and carbonate. In his textbook of 1903, Hoppe-Seyler gives the method of precipitating the protein with acetic acid, and the globulin with ammonium sulphate. Sodium chloride and sodium sulphate have also been much used. Three fractions were at first separated with different concentrations of the salt solutions. Euglobulin was precipitated with saturated sodium chloride, half saturated magnesium sulphate or one-third saturated ammonium sulphate; pseudoglobin with saturated magnesium sulphate or half saturated ammonium sulphate, and albumin only with saturated ammonium sulphate. Later analyses have established the following range of precipitation of the protein fractions with ammonium sulphate solutions (Howe):

Fibrinogen 30 per cent saturated
Euglobulin 30-36 per cent saturated
Pseudoglobulin I 36-44 per cent saturated
Pseudoglobulin II 44-50 per cent saturated
Albumin 50-100 per cent saturated

Jolles devised a gas volumetric method for determining the protein nitrogen in whole blood, requiring only 0.2 cc. The blood was oxidized with potassium permanganate, and a proportion of the nitrogen was driven off as gas, amounting to 80.5 per cent of the nitrogen as determined by the Kjeldahl method.

A new impetus was given to the study of the serum proteins when Strubell, in 1901, and Reiss a few years later, discovered that the refractive index could be used in their measurement. Strubell first used the index of refraction to determine the osmotic pressure of salt solutions and urine, as substitute determinations at the freezing point. The method had the advantage of requiring only one drop of solution. Later, in applying it to blood serum, he decided that the index was proportional, not to the osmotic pressure, but to the protein content of the serum. The change in refraction caused by the salts and other nonprotein substances of the serum was found to be small in comparison with that caused by the proteins, and was fairly constant for all persons. By making determinations of a number of solutions of different strength, Strubell calculated the change in refractive index caused by 1 per cent of protein. Then, the index of the unknown serum, less that of distilled water and of the nonproteins, divided by the change for 1 per cent, gave the percentage of protein in the serum.

A year later, Reiss began his extensive investigations with the refractometer. He separated the protein fractions, and determined the refractive index for each, finding it greater for globulin than for albumin. By comparing the indexes for different amounts of protein, he determined anew the change for 1 per cent, 0.00172. Strangely enough, this was lower for total protein than for either of the fractions

separately. He used a constant value for the nonproteins, 0.00277, assuming that it did not vary appreciably except in uremia. Reiss' values in normal persons, from 7 to 9 per cent of protein, were admitted to be a little higher than those obtained by the Kjeldahl method, but were thought accurate for making a series of observations on one person.

Doubts as to the accuracy of the refractometric method were raised in 1907 by Chiray and Demanche. Comparing it with the gravimetric method, they found irregular differences of from 1 to 17 per cent which they attributed to the effect of other constituents of the serum. Soon afterward, on the other hand, Widal, Benard and Vaucher made comparative tests with the Kjeldahl method and found differences of only 0.6 per cent. Shorer pointed out that the difference in refraction of the albumin and globulin fractions led to inaccurate results when the normal relation between the two was changed, and concluded that the method should be used only for comparing a series of results in the same patient. Still later, Rowe (1916) and others found that the values of the index assumed by Reiss for the nonproteins were incorrect. Reiss acknowledged the justice of Shorer's criticism, but upheld the value of the method for constructing serum protein curves for patients with various diseases. Strauss and Chajes made further examination to determine the accuracy of the refractive index as a measure of protein content. They found that temperature, sugar and urea up to 1 per cent of the serum, made little difference, and concluded that the refractometer was sufficiently accurate for clinical purposes. Tuffier and Mauté and Kämmerer and Waldemann compared the refractometric technic with the chemical method, and found good agreement between them.

Robertson devised a microrefractometric method for determining the protein fractions as well as the total protein, using only 0.5 cc. of serum. He eliminated the chief defects of Reiss' procedure. The value for the nonproteins was determined for each serum after the protein had been precipitated. The albumin was measured after the globulin was precipitated with ammonium sulphate, and the globulin by difference. The method was published in 1915. Rowe used this method in his extensive investigations, except that he used a constant value, 0.00175, for the refractive index of the nonproteins when there was no reason to expect that they were increased. In 1915, working with Tranter, he found the average protein in healthy persons to be 7.94 per cent; albumin, 6.2 per cent, or 78 per cent of the total; and globulin, 1.74 per cent, or 22 per cent of the total. In 1916 he published a review of the literature up to that time, a critical review of methods and the results of his own investigations. The normal averages

of this series were: protein 7.5 per cent, albumin 5.6 per cent and globulin 1.9 per cent, or 25.5 per cent of the total protein.

Autenrieth, in 1917, described a colorimetric method for measuring the serum albumin and globulin based on the biuret test for protein. He separated the fractions with ammonium sulphate, alkalinized the solutions, diluted twenty times, added copper sulphate and compared the colors with standard solution of the proteins. The results agreed well with those obtained by the gravimetric method. On the same principle. Wu separated the fractions with ammonium sulphate, and measured the amount of protein in each by the color reaction with phosphomolybdic-tungstic acid. His figures were a little lower than previous ones, 6.94 per cent for the average serum protein in healthy persons.

Holm and Tomasson described a method in which the diluted serum was poured in a layer on top of nitric acid, and from the highest dilution in which a white ring was formed, calculated the percentage of protein in the fluid. They found figures in normal persons varying from 5.55 to 8.77 per cent.

Of the more recent methods for determining the serum proteins, that of Naegeli and his pupil Rohrer has been most used. The viscosity of albumin and globulin solutions with the same refractive index differ, the globulin being about twice as viscous as the albumin. Heyder, in 1915, and later Rohrer, succeeded in constructing curves, using the refractive index and viscosity as coordinates, for solutions containing different proportions of albumin and globulin. From Rohrer's table, it was possible to read off the relative composition of a serum, if the refractive index and viscosity were known. In 1922, he made a number of determinations in this way, and found close agreement with the other methods. Alder used Rohrer's method in 1919 and found that the albumin in healthy persons varied in amount from 55 to 80 per cent of the protein. The daily changes in the same person were slight.

Rusznyak, in 1923, first used the nephelometer, calculating the relative amounts of the different protein fractions from the cloudiness which developed on the addition of ammonium sulphate solutions of different concentrations. By measuring the total protein by other methods, the absolute amounts could be reckoned.

Betz and Kaufmann used the interferometer for comparing the refraction of a standard with that of an unknown solution, and calculated the percentage of protein from the refractive index as described by Reiss. The new method agreed well with the refractometer and with the chemical methods, the greatest difference between them being 0.85 per cent. The figures with the interferometer were usually a little higher than with the refractometer, and the authors regarded the former as the more accurate instrument.

A return to the older chemical procedures took place with the work of Cullen and Van Slyke in 1920. They used calcium chloride to precipitate the fibrinogen and ammonium sulphate for the globulins. The nitrogen was determined for the whole serum, for the nonprotein substances, and for the three protein fractions according to the Kjeldahl method. Howe, in his work with calf blood, followed a similar procedure, but used sodium sulphate for separating the protein fractions. Two further modifications for determining the globulin fraction more simply were published by Henley in 1922.

A few further criticisms and improvements of former methods have been made in recent years. Neuhausen and Rioch amended Reiss' procedures by using 0.00194 as the refractive index for 1 per cent combined protein instead of 0.00172, and obtained much better agreement with the chemical determinations. Schretter again increased the index to 0.00202, on the basis of comparison with other methods. He also called attention to the possibility that the index may vary in different serums, partly as the result of technical errors and partly because of changes in the albumin-globulin relation in pathologic conditions. Caution is necessary, therefore, in the interpretation of results.

Berger and Petschacher compared the refractometric methods of Reiss and Rohrer and Robertson with the Kjeldahl determination of nitrogen in the fractions separated with magnesium sulphate. The results by Reiss' method were too high—as much as 1.5 per cent. Rohrer's methed seemed accurate in normal persons, but in pathologic conditions it frequently gave too high a proportion of globulin. Robertson's method was found to be the most accurate, in agreement with the chemical analysis. Frey also found lack of agreement between the results with the refractometer according to Reiss and the viscosimeter according to Rohrer, and chemical determinations. He concluded that the methods of Reiss and Rohrer were not reliable. Gutzeit did not try Robertson's refractometric method, but after extensive investigations of the refractometer as used by Reiss, the viscosimeter and the interferometer, he decided that these instruments did not give accurate measurements of the serum proteins, chiefly on account of the varying albumin-globulin relation. He considered precipitation of the fractions and determination of the nitrogen in each by the micro-Kjeldahl method as the only reliable procedure for clinical work. Chalier, Boulud, and Chevallier came to the conclusion that the refractometer could be used except in uremia, when the results were much too high, but that the viscosity of the serum did not correspond to its protein content. Kollert and Starlinger, using the refractometer in their earlier work, later decided that precipitation with salt solution, followed by actual weighing or nitrogen determination chemically was the more exact method.

Leendertz suggested as a measure of serum lability the quotient obtained by dividing the "labile globulin" (the fraction precipitated by dilution and acidification with weak acetic acid) by the serum protein, both expressed as coefficients of refraction. In normal persons, this quotient appeared always to be below four. Values above this, indicating an increase in the lability of the protein, were found only in the presence of disease, with cellular destruction, exudation or extensive suppuration. Leendertz found differences between the protein content of serum from plasma and from whole blood, ranging from 0.17 to 0.54 per cent, and suggested that it was more accurate to use the former.

The serum proteins vary under different physiologic conditions. Each species of animal is characterized by its own normal serum composition, as has been shown by a number of investigators (Lewinski, Joachim, Abderhalden, Robertson, Woolsey, Thompson, Jewett, Briggs, Howe in 1925). Thus, in man, sheep, goat, rabbit, dog, guinea-pig and rat, the albumin fraction is the greater, while in horse, hog and cow the globulin fraction is equal to or greater than the percentage of albumin.

Variations with age have been demonstrated both in animals and in man. C. E. Wells found an increase in serum protein in rabbits of from 5.5 to 8.8 per cent between the twenty-first and one hundred and fortieth days, followed by a slight decrease. In rats, Toyama showed a rapid increase in protein during the suckling stage, a slow increase at puberty and constant value in adults. Handovsky found lower total protein and globulin in calves than in cows, with occasional absence of euglobulin in the former.

Reiss made the first measurements on the blood of human infants in 1909, finding from 5.5 to 6 per cent of protein at birth, and an increase to the adult value between the sixth and tenth months. Similarly, Zangemeister and Meissl reported 5.16 per cent, Landsberg 5.05 per cent and Bauereisen 4.94 per cent at birth. Rusz determined the refractometric index in infants, finding it low at birth, decreasing farther during the first week, and then increasing throughout the first year. Utheim, in 1920, found 6 and 6.5 per cent of protein in the serum of infants born at term, and less (3.94 per cent) in premature babies. It remained low for ten or eleven months, and reached the adult value about the fifteenth month. The same results were obtained by Duzar and Rusznyak, using the nephelometer. The following values for serum protein at different ages were given by Lederer in 1924:

Under 3 months 5 per cent
From 3 months to 2 years 5.5 to 6.5 per cent
From 2 years to 6 years 6.5 to 7.8 per cent
From 6 years to 14 years 7.5 to 8.2 per cent

A decreased proportion of globulin in the blood of infants was reported by Naegeli, Schiff and Roser, Howe, and Lewis and Wells. Howe demonstrated the absence of pseudoglobulin I and of euglobulin in the serum of new-born calves. On a diet of colostrum, the missing globulins increased rapidly and then fell somewhat, while in the absence of colostrum there was a gradual but steady increase, until the adult value was reached at the eighteenth to twenty-second month. The serum albumin, also low in content at birth, rose to the adult value in two weeks. Lewis and Wells found absence of euglobulin in the blood of human infants, with the other protein fractions as in the adult, and called attention to the rôle of colostrum in supplying the missing fraction.

Daily variations in the same person appear to be slight. Heudorfer studied the serum protein refractometrically under normal conditions, and found the range to be from 7.2 to 9.0 per cent, slightly higher after the patient arose and ate than it was while he was in bed before breakfast. Variations from day to day were slight, and change did not occur after fluids were taken. Martius' work showed little variation in the refractive index at different hours of the day, but Reiss thought it should be taken at the same hour (in bed before breakfast) to eliminate the influence of food and exercise. Thus, Böhme in 1910 found increases from 8.56 to 9.74 and from 8.25 to 9.51 per cent after exercise. Slight increases occurred even after the patient got out of bed. Böhme attributed the change to loss of water from the blood. Food and liquids did not make any immediate difference in the protein percentage, and only slight variations were found during the day, and on different days, in the same person. Carbon dioxide caused a rise in protein content and a fall in oxygen, but the content was the same in arterial, venous and capillary blood.

In 1916, Rowe determined that venous stasis caused an increase in the protein content of the serum. An elastic band placed around the arm for forty minutes caused a rise of from 7.2 to 12.16 per cent. The albumin made up the greater part of the increase. Schwenker had previously investigated this subject and shown that constriction for twenty minutes caused an increase of 3 per cent in the refractive index. Rowe suggested the escape of fluid from the capillaries and increased carbon dioxide in the blood as explanations for the rise. Muscular activity increased the serum protein. Diet did not have an immediate effect, but after several days of high protein diet, the serum protein content increased slightly. Keeping serum on ice for forty-eight hours did not change its composition. Naegeli reported in his textbook that the albumin-globulin ratio was constant during the day, was not affected by food, water or exercise and was the same in arterial and venous blood in healthy persons. In hunger, cachexia and heart and respiratory diseases, however, the globulin content was higher in venous than in

arterial blood. Gollwitzer-Meier and Kroetz found the protein content lowered during sleep. Handovsky reported a seasonal variation in animals, with albumin relatively higher in summer, and globulin in winter.

Differences in the serum protein of the two sexes have not been reported. Martius found a fall in the refractive index at the beginning of menstruation, while Enfinger and Goldner found the globulin increased, as much as double its normal value, with a corresponding fall in the albumin.

Changes could not be shown during pregnancy by Lewinski, or Scipiades and Farkas in women, or by Howe and Sanderson in cows. On the other hand, a number of workers reported a low protein content. Thus, Zangemeister found 6.32 and 6.68 per cent during pregnancy and labor, contrasted with from 7.94 to 8.45 per cent in normal women. With Meissl he compared the protein of mothers, average 6.79 per cent, with that of new-born infants, average 5.16 per cent. Landsberg also demonstrated a slight decrease: normal women, 7.01 per cent; pregnant women, 6.5 per cent. The fibrinogen was higher than normal. In cases complicated by albuminuria and edema, the protein content was 5.65 per cent. Loeper, and later Dienst, reached the same general conclusion, and Dienst reported a further drop in protein, especially in globulin, with complications such as nephritis and eclampsia. An increase in the proportion of globulin during pregnancy has been shown by Rusznyak, Barat and Kürthy, and by Hafner.

Plass and Bogert made a more extensive study. During the first two months of pregnancy a change did not occur, then there was a gradual fall in protein content until the fifth month, and during labor it rose to nearly the normal value. In the first days of the puerperium, a second drop occurred, with a return to normal in one week. In late toxemias, the decrease in protein was exaggerated. The authors regard these changes as due to dilution of the blood. Coetzee found the usual decrease, more marked in the globulin fraction, and increase in fibrinogen. From this he concluded that the change could not be caused by absorption of foreign protein from the fetus, since injections of protein are followed by an increase in globulin. Of the complications of pregnancy, albuminuria and nephritis were associated with increase in the globulin fraction, toxemia with no change and eclampsia with a definite absolute and relative decrease. Kürthy also found increased globulin in a case of nephritis of pregnancy. Preissecker, on the contrary, found the protein content slightly increased in normal pregnancy, but in eclampsia at the lower margin of normal, with a relative increase of globulin. In Hafner's work, also, the protein was increased.

A controversy over the effect of antipyrine, of interest because of its effect on metabolism, was started when Cervello in 1910 reported a marked increase in protein and in the globulin fraction in dogs after

large doses of the drug. The following year he found that smaller doses were not effective. Breinl repeated the work in 1911, and found the globulin increased, and the albumin correspondingly diminished. Serum mixed with antipyrine in vitro underwent the same changes, from which fact he concluded that the albumin had actually changed into globulin. Some years later, Hanson and McQuarrie determined that large doses of antipyrine and related substances, also quinine, sodium cacodylate and thyroid extract, did not cause a change in the serum proteins. They concluded that the quantity of albumin and globulin in the serum is independent of the rapidity of nitrogen metabolism. Of other drugs investigated, according to Ellinger, caffeine and urea caused an increase in protein content with a fall in viscosity, while merbaphen had the opposite effect.

Between 1900 and 1909, a number of experiments were made to determine the effect of salt and water on the serum proteins. Magnus found that injection of either hypertonic or hypotonic salt solution caused a diminution of the protein, which he attributed to the passage of protein out of the vessels. Loeper showed the same for hypertonic glucose solution. According to Benčzur, also, the blood was diluted after salt solution was given intravenously or after the ingestion of 12 Gm. of salt, and its content returned to normal in five hours. Engel and Scharl, and Plehn concluded that drinking even large amounts of water did not cause a change in blood concentration, while Marx, in 1926, reported dilution of the blood as measured by hemoglobin, protein and chlorides, in normal persons. Hot baths in fasting subjects were also followed by dilution of the blood. In persons with renal insufficiency, the composition of the blood did not change under these conditions. Lasch, in the same year, reached somewhat different conclusions. In normal persons after the ingestion of large amounts of water, he found a rise in total protein, with a relative increase in globulin during the next twenty-four hours. In persons with disease of the kidneys, on the other hand, the protein content fell, while the proportion of globulin increased. Lasch thought with Nonnenbruch and others that the protein content could not be used as a measure of the blood concentration or of its water content.

The effect of starvation on the serum proteins and their behavior during bleeding and transfusions have been extensively studied in animals. C. E. Wells fed animals diets of varying composition without altering the composition of the blood. Robertson (in 1912) found the protein content increased during starvation, the albumin in some animals, the globulin in others, while Briggs reported a constant increase in the albumin fraction.

As long ago as 1864, in connection with the origin and function of serum protein, Panum studied the blood of dogs during starvation,

and discovered that it decreased with inanition, and increased again after blood transfusion. He concluded that the protein was used in nourishing the body. In similar work with snakes, Tiegel showed that practically all the serum albumin disappeared during starvation and reappeared when the animal was fed again. He regarded this as evidence for the origin of albumin from the food and its consumption in the course of metabolism. The globulin did not undergo this change. Salvioli, on the other hand, found the relative proportion of albumin in dog's blood increased during starvation, and the globulin increased during digestion. Burckhard confirmed the increase in globulin and decrease in protein during starvation. After bleeding, the amount of protein and of albumin was decreased, while the globulin underwent irregular fluctuations.

Later, Lewinski found the globulin of dog's serum increased but not any regular change in the albumin during starvation. Wallerstein obtained the same result in rabbits. Githens' work in 1903 showed an increase in globulin and a decrease in albumin during underfeeding in dogs, with a return to the normal relations after a full diet. After rapidly repeated bleedings, the protein was low and the albumin relatively high. He explained these changes by assuming that, since globulin is nearer in composition to the protein of the organs, it enters the blood from that source during starvation. Albumin, closely related to the food proteins, is made up more rapidly, after loss through bleeding, and is quickly restored, after starvation, by a full diet. Similarly, Schoeneich found a decrease in the serum protein during starvation, although in extreme starvation this effect was masked by the resulting dehydration. Thirst and diuresis were both followed by a relative increase in protein through diminution of the water content, and after bleeding dilution of the blood was present for a short time.

Morawitz, in 1905, studied the renewal of serum protein after bleeding. He bled starving dogs at intervals until the protein content was reduced from 6 to 2 per cent. When food was not given, the protein gradually increased, first the albumin and then the globulin, until the globulin was above normal. He regarded the rapid renewal of albumin as evidence that it is stored somewhere in the body, to enter the blood when needed, but that the globulin must be formed anew. Later, in 1909, he reviewed the methods of separating the protein fractions and commented on the frequent association of leukocytosis and increase in euglobulin, of decreased total protein and increased globulin.

Kerr, Hurwitz and Whipple studied the regeneration of the serum proteins by repeatedly bleeding dogs and returning the washed corpuscles into the vein. In fasting animals, it took more than ten days to restore the protein after a depletion of from 40 to 50 per cent. The globulin was

restored more rapidly than the albumin. Regeneration was more rapid on an adequate diet, especially one containing a large amount of meat, but, even so, from five to eight days were necessary. About 1 per cent was restored in the first twenty-four hours, regardless of diet. These results indicate that the serum proteins are not intermediate products between the food and the tissues, since regeneration was slow even on a meat diet, but that they must be formed from body protein. Injury to the liver was found to retard the restoration, indicating that this organ is concerned in maintaining the serum protein level. Later, Smith, Belt and Whipple investigated the effect of a single large bleeding, and discovered that a rapid initial regeneration took place in the first fifteen minutes, while the rate thereafter was much more gradual. This would indicate a reserve supply of protein that can be thrown into circulation hurriedly in an emergency.

Data as to the effect of roentgen rays on the serum proteins are meager and not in agreement. Herzfeld and Shinz found the refractometric index decreased in twenty-nine of thirty-six persons following irradiation, and a relative increase in globulin. Löhr agreed with them, and suggested that the "absorption fever" following the administration of roentgen rays or radium was caused by protein intoxication from destruction of serum protein. Kroetz, however, found the index increased in all cases, and concluded that there was an increase in the total protein, or a qualitative change in its composition.

The most significant and widely investigated variation in the serum proteins occur in the course of infection and disease. As early as 1883, Hofmann made the observation that the serum of sick persons contained relatively more globulin than that of healthy persons. The quotient, albumin divided by globulin, in health varied from 1.85 to 2.54; when it fell below 1, illness was present, and usually severe.

In the acute infectious diseases, the change most frequently found is a decrease in protein, with a relative increase in the globulin fraction. Thus, Becquerel and Rodier observed a low protein content in endocarditis, typhoid and rheumatic fevers, pneumonia and severe puerperal sepsis, while Mya and Viglezio, using Pohl's method, noted an increase of globulin from the normal figure, 2.43 per cent, to 3 and 3.5 per cent in pneumonia, tetanus and other diseases. Von Jaksch, another early investigator, used the Kjeldahl method to determine the serum protein, normal 8.86 per cent, and the whole blood protein, 22.6 per cent. He found the whole blood protein decreased in acute infections and in typhoid fever, while the serum protein remained approximately the same. The data of Limbeck and Pick showed from 3.25 to 5.66 per cent of serum protein in the presence of infectious diseases. However, their normal value, obtained by precipitating the protein with alcohol and the globulin by Pohl's method, was somewhat lower than usual.

from 5.4 to 7.43 per cent. Erben, from his extensive investigations in 1900, concluded that the increase of globulin in infections was due to its greater resistance to toxins.

Reiss and Oppenheimer, in 1909, found slight dilution of the blood (6.2 per cent protein) with increase in body weight during the febrile period of uncomplicated scarlet fever, with a return to normal and loss of weight in convalescence. Before the beginning of a complicating nephritis, there was a second drop in the serum protein content. This preceded the clinical signs, and was regarded as a method of predicting nephritis. Recently, Steiner pointed out that the fibrinogen could be used for the same purpose. It was found in large amounts at the onset of the disease, decreasing gradually in uncomplicated cases. It increased again in complications, sometimes preceding the clinical signs by two days. Kalser and Löwy, on the contrary, did not find regular changes in this disease. An increase in protein content usually occurred during convalescence, but sometimes also before the beginning of complications, even of nephritis. They concluded that the determinations were not of much value in scarlet fever.

Reiss also reported a low protein content in pneumonia and typhoid fever; Engel, and Kammerer and Waldemann reported the same in the acute infections. Loeper found the decrease proportional to the length of the illness, and most marked in typhoid fever. Peters, Eisenman and Bulger studied the plasma protein, normally from 6.41 to 7.98 per cent, and found it normal or slightly above normal in five severe, acute infections. The globulin increase in acute febrile diseases was again confirmed by Rusznyak, Barat and Kürthy, using the nephelometer. They found the albumin increased in encephalitis.

In 1909, Sandelowsky used the refractometer to examine changes during fever in patients with pneumonia. He found, in most cases, a gain in body weight and a decrease in serum protein during the fever, as a result of the retention of water; but sometimes, when tissue destruction was more marked, both body weight and serum protein decreased. Later, he showed that the protein content of rabbits' serum decreased when they were heated artificially. He attributed the retention of water during fever to impairment of the excretion of salt. Rowe's results in pneumonia were similar; he found the protein reduced to 6.2 per cent with 40 per cent of globulin; and in other infections there was a similar increase in globulin without as marked reduction of total protein. Like Sandelowsky, he attributed the reduction of protein in fever to the retention of water.

According to Achard, Touraine and St. Girons, the protein content went through four regular phases in the presence of infectious diseases. During the febrile period there was a drop, the degree and duration depending on the severity of the illness. Just before the crisis, the

protein was at its lowest level. During defervescence it increased so that it was sometimes above normal in convalescence. Complications were associated with a second fall, or absence of the usual rise. Similarly, Berger and Untersteiner described three phases through which the serum protein passed, following an experimental infection in man (malaria therapy for paralysis). During the incubation period, the protein was low, with relatively increased globulin. During the fever, the relations were normal at first, and toward the end the preceding change occurred in more marked form. Lastly, during convalescence, the protein and albumin content remained low for several days and then increased. The decrease in protein and albumin was regarded as an accompaniment of the lesion caused by the general injury, and the later increase as a manifestation of repair. Schindera found much the same results in acute infections, such as scarlet fever and pneumonia.

Nine cases of kala-azar, investigated by Wu, showed an increased serum protein content (the highest 10.54 per cent), with a predominance of globulin.

Of the chronic infections, tuberculosis and syphilis have received most attention. The earlier data concerning tuberculosis indicated a reduction in serum protein (Becquerel and Rodier, Strauer in active processes, Martius, Schindera and Erben), and a relative increase in the globulin fraction (Andral, Schindera, Bircher, Erben, Rusznyak, Barat and Kürthy).

Engel, in 1907, was the first to find the serum protein content as determined by the refractometric index above normal, in some cases of pulmonary tuberculosis, although the index was low in other cases, with marked emaciation. Alder's study, in 1920, with the refractometer and viscosimeter led to the same conclusion. In mild tuberculosis, the protein content fell within normal limits. In severe cases, but with good nutrition, the value was high, over 9 per cent, while in severe cases with marked cachexia it was normal or subnormal. Alder suggested the bone marrow as a site of origin for the serum proteins, overstimulation accounting for the rise and later fall in their concentration. The relation between the albumin and globulin, normal in mild cases, was shifted to the advantage of the globulin in patients who were severely ill, over half of the latter having more than 50 per cent of globulin. The increase apparently depended on the activity of the process and was highest in the cachectic patients with a low serum protein content. Alder thought that the qualitative change was of some diagnostic and prognostic value in tuberculosis, but that the quantitative differences were too slight for practical application.

Durand confirmed Alder's work, finding the protein increased to 9.4 per cent in severe cases, with evident toxemia, and the globulin from 50 to 75 per cent of this. Petschacher also reported a high

protein content in tuberculosis, and a relative increase of the globulin in direct relationship to the activity and extent of the disease process. Leendertz could show correspondence between the height of his quotient for serum lability, and the severity of the process and amount of tissue destruction. The quotient was increased from the normal 4 to 10 or 12 in active febrile cases. Finally, in 1925, Sussmann concluded from the work of the last century that the fibrin, globulin and total protein were all increased in a group of tuberculous persons, those with severe active, toxic processes. He did not consider this change to be of diagnostic value as it occurs only in severe, frank cases, and is not specific for tuberculosis. He described various serologic tests that have been proposed for the disease, based on the increase of coarsely dispersed protein in the serum.

In 1920, Meyer-Bisch reported observations on the relation of body weight and serum protein, supposed to be characteristic of tuberculosis. He reported an evening drop in serum protein, with a rise in body weight, owing to the retention of water. The same changes followed injections of tuberculin. Salomon, in 1926, was unable to confirm either of these observations, and explained the evening increase in weight on the basis of food intake. Frisch and Starlinger, also, did not find constant changes following injections of tuberculin.

The blood proteins in syphilis have attracted a good deal of attention, and some contradictory results have been reported. Jolles and Oppenheim (1903) did not find any change in the protein content of the blood. Klausner demonstrated increased protein in the serum of syphilitic patients by obtaining a precipitate on the addition of distilled water. A precipitate was not obtained with normal serum. Elias, Neubauer, Porges and Salomon thought that the foregoing reaction might be explained by the decreased stability of globulin in syphilis. Noguchi, in 1909, determined the globulin in syphilitic serum by precipitation and weighing, and found it to be increased in untreated patients. Serums from persons apparently healthy, but with strongly positive Wassermann reactions, also contained increased globulin. Noguchi concluded that the change ran parallel to the Wassermann reaction. Müller and Hough found the euglobulin high in syphilis, but could not establish any correlation between this and the Wassermann test. Winternitz, precipitating the different kinds of globulin with ammonium sulphate, found the fibrinogen increased, the globulin less so and the albumin unchanged. Later, using the refractometer, he confirmed the increased fibrinogen content, and was able to show a high total protein content, especially during the secondary stage. The increased protein corresponded to the positive Wassermann reaction. Rowe found the total protein unchanged, and the globulin slightly increased from 25.5 to 33.7 per cent, but did not agree with some of the aforementioned investi-

gators that the Wassermann reaction depended on increased globulin in the serum. Tokuda, using Robertson's method in 1921, reported an average of 6.95 per cent of protein with 21 per cent globulin in the serum of syphilitic patients. The protein was somewhat higher during the secondary stage, and showed a tendency to decrease with treatment. Wu, using his colorimetric method, found the protein increased. Bircher and McFarland showed the usual predominance of globulin in syphilitic serum, 90 per cent of the patients having over 50 per cent before treatment. They regarded this change in the serum protein as more constant than the Wassermann reaction and as important corroborative evidence of syphilis.

In the field of pediatrics, especially of nutritional disturbances, study of the serum proteins has yielded some interesting results. Reiss found that in simple diarrhea, there was an increase to 8.5 or 9 per cent from loss of fluids, while in severe intoxication with loss of tissue as well as water, the previously high serum protein fell abruptly. In chronic nutritional disturbances, the protein was approximately normal; in edema it was low. Reiss found the refractive index of value, if used in conjunction with the body weight, in determining the degree of dehydration in infants, and also in the prognosis of nutritional disturbances.

Salge was able to show a decrease in serum protein in severe atrophy following overfeeding with carbohydrates (from 3.94 to 5.33 per cent), and an increase in intoxication from 7.72 to 11.046 per cent). In moderate degrees of atrophy the protein was variable, from 5.88 to 8.2 per cent. In chronic nutritional disturbances, the value was frequently normal, becoming low with starvation and sufficient water intake, or high with diarrhea. Berend and Tezner confirmed the results in intoxication, and pointed out that the serum protein could be decreased as much as 1.2 per cent of its original value by the oral administration of salt solution. Utheim attributed the low protein in decomposition (4 or 5 per cent) partly to lack of protein in the diet and partly to the lack of power to build up protein in the body. Low values were found in nephritis and exudative diathesis also. Schiff and Roser investigated the albumin-globulin relation in infants. Normally, the globulin formed from 10 to 40 per cent of the protein; it was unchanged in acute infections and anemia, but increased in chronic infections such as syphilis and tuberculosis, to from 40 to 90 per cent. The albumin was at the higher margin of normal (90 per cent) in prematurity, exudative diathesis and rickets.

Marriott studied the changes in the blood in anhydremia from various causes, finding an increase in the specific gravity, hemoglobin content, cell count and serum proteins. The latter increased from 50 to 100 per cent above the former value in some instances in which the

anhydremia was brought about suddenly. Severe malnutrition, with depletion of the protein stores of the body, is accompanied by reduced plasma protein according to Peters, Wakeman and Eisenman. They suggested that low protein in persons without disease of the heart or kidneys is an indication of previous protein starvation and is a contributory cause of edema from cachexia or starvation. Previous to this work, Knack and Neumann had shown that the refractive index was low in persons suffering from edema caused by famine during the war. Bakwin, Astrowe and Rivkin investigated the effect of the transfusion of blood in malnourished infants, finding only slight changes in the plasma protein. Apparently, this element leaves the circulation along with the plasma fluid. The protein approached normal gradually, however, as the clinical condition improved.

Diseases of the blood were first investigated by Becquerel and Rodier, who found the serum protein normal in plethora, chlorosis and secondary anemia. However, later work has shown that the protein content is low in chlorosis (Heudorfer, 5.83 per cent; also Maxon, Kammerer and Waldemann and Engel), while Naegeli reported no change in the albumin-globulin ratio. Numerous determinations have been made in secondary anemias. According to Limbeck and Pick, the protein diminished after hemorrhage, returning to normal in forty-eight hours. Loeper found a drop from 4.9 to 2.5 per cent, following repeated bleedings in rabbits. Other experiments in bleeding animals have been mentioned previously. Von Jaksch and Jolles found the whole blood protein markedly reduced in anemia, as one would expect, with the serum protein frequently normal. Maxon, Grawitz, Engel, Kammerer and Waldemann all reported low protein values, and Peters and his associates found it low in half the patients investigated. A shift in the fractions in favor of the globulin was indicated by Naegeli and by Rusznyak, Barat and Kürthy.

Most of the work on pernicious anemia indicates a low serum protein content, although Grawitz found normal values, in contrast to his results in secondary anemia. Askanazy detected a reduction of the serum solids. Erben's study revealed 5.2 per cent of protein, with albumin relatively increased to 4.2 per cent. He suggested that atrophy of the gastric and intestinal mucosa might account for the failure to form globulin, which is a higher protein than albumin. Kahn and Barsky's results were much the same, from 5 to 6 per cent protein; also Reiss', from 5.4 and 5.1 per cent; Heudorfer's, 6.01 per cent, and Rowe's, 5.8 per cent in the most extreme case. Martius reported normal results in mild cases, and the usual reduction in severer ones. The relative increase of albumin, noted by Erben, was confirmed later by Naegeli, but not by Rusznyak, Barat and Kürthy, who considered the ratio normal in pernicious anemia.

In leukemia, Freund and Obermayer did not find any change; Jolles noted a decrease in the whole blood protein; Kammerer and Waldemann found a decrease in serum protein, and Heudorfer observed a decrease in some cases. Kammerer and Waldemann also reported the protein content low in hemophilia and hemorrhagic diathesis although Rowe found it normal in the former, while Betz and Kaufmann obtained an increase, 9.57 per cent, in polycythemia.

In diseases of the liver, Jolles found the whole blood protein low in cirrhosis and catarrhal jaundice, while Gilbert and Chiray, and Grenet found the serum protein low in cirrhosis with ascites and liver insufficiency. The refractometric index was high in a case of hypertrophic cirrhosis reported by Engel, normal in three cases of disease of the liver reported by Peters and his associates. Rusznyak and others detected an increase in the globulin fraction in obstructive icterus and disease of the liver, and this observation was confirmed by Fillinski in 1925. In mild disease, the globulin made up from 40 to 50 per cent of the protein, in moderate cases from 50 to 60 per cent and in severe cases from 60 to 70 per cent, or even higher. He thought that the globulin increase in nephrosis and infectious diseases might be explained on the basis of injury to the liver.

Limbeck and Pick studied five cases of diabetes, discovering a low serum protein content in all. The range was between 1.54 (the lowest value in any condition) and 4.42 per cent. Jolles confirmed the reduction for whole blood protein, while Mya and Viglezio, using Pohl's method for precipitating globulin, discovered an increase from 2.43 to 3 or 3.5 per cent. Engel disagreed, reporting a high refractometric index. Later work has demonstrated the correctness of both these apparently contradictory results. Reiss used refractometry, correlated with the body weight, to determine varying conditions of water retention and excretion in this disease. The sudden temporary changes in weight were accompanied by inverse changes in protein content. Since the drinking of large amounts of water causes little change in the blood concentration of healthy persons, Reiss concluded that there was injury to the kidneys in diabetes, manifested by varying retention and loss of water. Peters, Eisenman and Bulger, in an extensive study, found that in mild cases, without ketosis or malnutrition, the protein was normal, and in severe diabetes with malnutrition it was usually low. With insulin therapy and improvement it became normal again. Some patients with severe toxemia and ketosis had relatively high plasma protein from loss of water. In diabetic edema, the protein was low. Widal, Abrami, Weill and Laudat described hydremia following the use of insulin in diabetic patients, with decreased serum protein in fourteen of nineteen patients so treated. Occasionally, edema was evi-

dent, but in most cases the retention of water was demonstrable only with the refractometer.

The change most frequently reported in malignancy is diminution of serum protein, although there are a few dissenting opinions. Strauer, Heudorfer, Kammerer and Waldemann, and Engel were all able to show the decrease. Reiss gave 3.9 per cent as the lowest value found by him in this condition. According to Erben, the reduction was slight, however, with a normal ratio between the protein fractions. Bircher, on the contrary, found the ratio much altered in favor of the globulin, this fraction making up more than 50 per cent of the total in all cases, and in one as much as 96 per cent. The shift was confirmed by Rohrer, whose determination showed that the globulin increased to from 60 to 90 per cent.

Loebner reported that the protein content was diminished in carcinoma, measured with the refractometer and viscosimeter, with a minimum value of 4.2 per cent, and an average of 7.3 per cent. This is hardly below the average for healthy persons. The globulin was relatively increased. Theis' averages, determined chemically, were: serum protein in patients with carcinoma, 6.8 per cent; plasma protein in patients with carcinoma, 6.3 per cent; plasma protein in other persons, 7.0 per cent. According to Loeper, Forestier and Tournet, on the contrary, the protein in persons with malignant tumors was frequently increased, in one instance reaching 11 per cent. The larger the tumor, the higher was the serum protein. The globulin fraction predominated, from 58 to 82 per cent, and a similar relationship was demonstrated in the protein of the tumor itself. Of twenty cases of cancer, Loeper and Tournet reported reduced protein in seven, probably as a result of hydremia and inanition, and increased protein in nine. After an operation for cancer of the breast, the content fell from 8.8 to 7.6 per cent. The last work on this subject, by Galehr in 1924, did not reveal a constant change in the total protein content, but usually a decrease. The range in forty-nine cases was from 4.4 to 8.5 per cent, and in none was the value above normal. The globulin made up more than 35 per cent of the protein in four fifths of the cases. The highest value occurred in patients with disintegrating tumors and wide metastases, corresponding to the lowest protein values. Galehr thought that both an increase in fluid and an actual decrease of circulating protein was involved.

In the field of surgery, Löhr's data is of interest, showing that after operations the fibrinogen and globulin were increased, while the total plasma protein remained the same. In two patients, one with osteomyelitis of the skull and the other with rupture of the stomach, the globulin made up 100 per cent of the plasma protein. Hueck also showed that the relative increase of globulin was constant after surgical operations, and corresponded fairly well to the increased rapidity of

sedimentation of the red blood cells. In the majority of cases he found the total protein reduced. The reduction was really greater than was indicated by the refractometer, as Hueck pointed out, since the index for globulin is greater than for albumin.

More recently, Achelis, interested in the importance of the serum proteins in surgical indications and prognosis, investigated numerous cases of inflammation, malignancy and tuberculosis by the Rohrer-Adler and Leendertz methods. In the inflammations he found a decided increase of globulin, and also in tuberculosis. Following his patients after operation, he observed that the ratio tended to return to normal with clinical improvement. A marked disturbance in the ratio was regarded as an indication for caution, for postponing or limiting surgical procedures, or for using extra care in the giving of anesthetics.

Loeper made some interesting studies on the serum protein in the retention of water from obstruction to the ureters. Working alone and with Achard, he ligated the ureters of rabbits, and observed a consequent drop in the percentage of serum protein. In man, the average value in conditions of ureteral obstruction was 4.8 per cent; in a woman with a uterine cancer completely obliterating the ureters the average value was only 1.2 per cent.

In disease of the cardiovascular system, the proteins were not affected by arteriosclerosis or hypertension according to Peters and his associates. Nägeli found a difference between venous and arterial blood, the globulin being higher in the former, in cardiac and respiratory disease. A slight reduction of total protein in these diseases was reported by Von Jaksch. Reiss' figures showed a normal refractive index in the presence of lesions of cardiac compensation, and a low index in cardiac edema, though not as low as in nephritic edema. Engel's results were approximately the same. Loeper, on the other hand, reported a high percentage of protein in cardiac edema, from 8.8 to 9.0 per cent. The chief interest in cardiac disease has centered around the behavior of the proteins in edema, which will be discussed later in connection with nephritis.

By far the most numerous and significant studies of the serum proteins concern their behavior in nephritis. Among the earlier workers in this field, Estelle, in 1880, reported on two cases of chronic nephritis. In one the albumin content was 3.06 per cent and the globulin content 5.44 per cent; in the other they were 1.8 and 3.6 per cent, respectively. Csatary, in 1891, also found increased globulin in four cases of chronic diffuse nephritis with edema, the albumin-globulin quotient in one being only 0.59. The total protein was low, varying from 3.4 to 4.2 per cent. In Limbeck and Pick's work in the same field, the total protein amounted to from 2.08 to 5.2 per cent, with the globulin content relatively increased. They suggested that the albuminuria was responsible for the

diminution of protein in the blood. Results similar to these have been reported again and again in later works, with but a few dissenting opinions. Thus, Freund (1895) maintained that the albumin fraction was relatively higher in chronic parenchymatous nephritis.

Part of Erben's extensive investigation in 1900 concerned disease of the kidneys. In a patient with subchronic nephritis, with edema and albuminuria, the protein was reduced (4.57 per cent), and the albumin fraction markedly so (only 0.004 per cent). In chronic parenchymatous nephritis the only change was again marked reduction of the albumin (to 0.29 per cent), and in contracted kidney with amyloidosis both total protein content and albumin content were slightly low. In the next few years, Jolles reported that the whole blood protein was low in chronic nephritis, but high in acute nephritis, Joachim studied a patient with chronic nephritis and edema whose serum contained 5.7312 per cent of protein, and Kammerer and Waldemann reported similar low values. Martius found the refractometric index high in uremia, but this result was probably caused by the retention of nitrogen. Chiray injected foreign proteins into animals, producing albuminuria, edema and cachexia, analogous to the symptoms of nephritis, and low serum protein.

One of the interesting studies on blood proteins in nephritis was made by Epstein. In 1912, he reported a reduction of protein in cardiac disease, the lowest being 3.6 per cent, with or without a relative increase of globulin. In respiratory disease, there was usually a slight reduction of the protein, with preponderance of globulin. Chronic parenchymatous nephritis, or nephrosis, showed a marked reduction in total protein, and marked preponderance of globulin, in one case 2.73 per cent protein, 2.59 per cent globulin and 0.133 per cent albumin. The protein in chronic interstitial nephritis was practically normal. In 1913, he did not find any change in prostatic hypertrophy unless associated with infection, and the usual globulin increase in localized infections of the kidney. In 1917, Epstein gave further figures on the serum proteins in nephrosis, protein 2.7 and 3.6 per cent, with 59 and 95 per cent of globulin, and described a type of diffuse nephritis occurring in pregnancy and diabetes that resembled nephrosis in this respect. He also related the edema of nephrosis to lowered osmotic pressure in the blood from loss of proteins, and suggested a high protein diet in the treatment. Epstein regarded chronic nephrosis as a metabolic disorder with marked changes in the composition of the blood serum (increased cholesterol, decreased protein), and the kidney manifestations as secondary to these.

Investigating various types of nephritis in 1913, Reiss found a low protein content paralleling increase in weight in acute nephritis with edema. In acute nephritis without edema, the concentration of the blood was slightly reduced, rising abruptly as excretion of salt and water

took place. The protein was always low in chronic nephritis with edema, and its remaining below normal when the edema disappeared could be used as a criterion of continued kidney insufficiency, with the inability to excrete salt and water normally. The index was normal in chronic nephritis without edema, except during uremia, when it was high because of retained nonproteins. Reiss considered the refractometric index of practical value in nephritis, correlated with determinations of body weight and salt excretion, to determine the functional condition of the kidneys and to detect the early retention of water. Early cardiac decompensation could also be detected in this manner.

In 1917, Rowe added some figures to his previous work. Chronic nephritis with edema was associated with the lowest total protein (from 3.8 to 5.3 per cent), with the globulin increased up to 50 per cent. In uremia there was little change; in nephritis without edema or uremia the globulin was increased and protein slightly decreased. In cardiac decompensation with or without edema the protein content was low, 5.9 per cent, although not as low as in nephritic edema, and the globulin was increased. Veil, in 1918, confirmed the many previous reports of low serum protein in glomerular nephritis with edema, and normal serum protein in primary or secondary contracted kidneys without edema, and Betz and Kaufmann confirmed the low serum protein in nephritis and nephrosis.

Comparisons of the serum in cardiac and renal edema led to opposing conclusions. Brandenstein, in 1904, found the protein content low in chronic parenchymatous nephritis with edema, normal in cardiac edema and slightly reduced in mixed forms. Strauss reached the same general conclusion, finding the refractive index markedly low in nephritic edema, and normal, or only slightly below normal, in cardiac edema severe enough to be fatal. The difference between the two types was great enough to be of diagnostic value. As a control for his experiments, Strauss showed that the refractive index in a normal person varied little from day to day. Reiss, Engel and Rowe also reported a slight decrease in cardiac edema, more marked in the renal type. In the work of Chiray, on the other hand, in agreement with Loeper, while the serum protein was low in nephritic edema, it was above normal in cardiac edema. He regarded the decrease in nephritis as due solely to retention of water and not to loss of protein. In the cardiac cases, he assumed that the sluggish circulation permitted filtration of water out into the tissues, causing a relative increase in the amount of protein. Contrary to these results and agreeing with the older investigators, Widal, Benard and Vaucher concluded that the protein was reduced in cardiac edema also. In one case they found 4.7 per cent of protein, increasing with improvement to 9.2 per cent, figures comparable to those found in nephritis with edema. Their determinations in nephritis

revealed the usual decrease in acute nephritis and in chronic nephritis with edema, both parenchymatous and interstitial. In the latter condition, they called attention to the permanently low protein level that may accompany permanent damage to the kidneys. By giving salt to persons with either cardiac or renal edema, they could cause an increase in body weight with a corresponding decrease in serum protein from the retention of water. By the refractometer they could distinguish true increases in body weight from those resulting from the retention of water.

Fodor and Fischer reported results in different types of edema. In nephrosis, syphilitic and nonsyphilitic, and in subacute, diffuse glomerular nephritis the protein content was low (from 3.2 to 5.91 per cent), and the globulin was relatively increased. In acute glomerular nephritis, the protein was only slightly reduced. Edema due to mechanical causes such as cardiac decompensation, was accompanied by normal, sometimes decreased, protein, with the globulin content slightly above normal. In edema from hypothyroidism the protein content was from 5.3 to 6.2 per cent, with the globulin always more than the albumin. Kisch, working on the same subject, found the protein low, from 4 to 6 per cent in nephrosis and amyloid kidney with edema. Contrary to the previous authors, he found a high protein content, 9.35 per cent in myxedema. In cardiac and nephritic edema, the proteins varied, normal or slightly below, the lowest value being 6.1 per cent. His work opposed the theory that edema was caused by low serum proteins.

Between 1920 and 1926 a number of studies of nephritis and related subjects were undertaken. Kahn, after measuring the protein content of the serum in twenty-three persons with chronic parenchymatous nephritis, failed to find one that corresponded to Epstein's nephrosis. He found the protein only slightly reduced and the globulin fraction never over 44 per cent. Nonnenbruch reported no constant change after injecting urea or giving it by mouth. Three nephritic patients with edema whom he examined had high serum protein. He accepted this observation as an indication that the edema was extrarenal in origin, based on vessel injury with consequent loss of water from the blood. In rapid loss of weight from excessive excretion of water, as from certain diuretics and from a dry diet high in salt, the proteins increased. Nonnenbruch thought this a real increase in amount of protein, not merely a relative change from loss of water from the serum. Taking water restored the protein to normal, however. Intravenous injections of salt solution and hypertonic sugar solutions were followed by increased protein percentages. Nonnenbruch made simultaneous erythrocyte counts to determine changes in the concentration of the blood, believing that it was measured more accurately by the red cells than by the proteins, which can pass in and out of the vessels. With Bogen-

dorfer, he called attention to the fact that the protein content, as well as cell counts, differs in capillary and venous blood. Bauer and Achsner disagreed with Nonnenbruch, finding the protein a better measure of blood concentrations than the hemoglobin content or red cell counts. They stated that protein passed through the vessel walls only in pathologic conditions, as in albuminuria. They found the same results following the administration of diuretics, increase in protein content, although diuretics given intravenously caused a fall from 6.336 to 5.728 per cent.

Continuing the work on edema, Beckmann reported a low protein content in edema resulting from chronic glomerular nephritis, disturbances of internal secretion and pernicious anemia, and normal protein in acute glomerular nephritis and cardiac insufficiency. He called attention to the difficulty of distinguishing a true decrease of protein from hydremia, and to the frequent lack of correspondence between the ultrafiltrability of the serum and its protein content, as a result of variations in the hydration capacity of the protein. Later, in 1926, Beckmann and others studied changes in the composition of the plasma following extirpation of the kidneys in dogs. An increase in the percentage of protein was apparent following the operation, but after measuring the plasma volume also, they concluded that the absolute quantity of protein was distinctly diminished, in one case almost halved. Of the protein fraction, the fibrinogen increased in all instances, and the albumin usually increased relative to the globulin.

Petschacher and Hönlingen, using Robertson's method, attempted to clear up the question of serum protein in nephritis. In acute nephritis they reported normal protein content. In chronic nephritis, the protein varied, low if the nephritic element predominated, and high if there was a tendency to secondary contracted kidney. The globulin was high. Cases of secondary contracted kidney with uremia showed normal protein, with slightly increased globulin. In nephrosclerosis and hypertension the protein was normal, or low if nephritic signs were present. Extrarenal edema was characterized by normal or slightly low protein, and increased globulin in the presence of infection. The authors attributed the change in nephritis to the accompanying infection. In nephrosis it appeared to be related to the albuminuria and edema, loss of albumin in the urine and the retention of water accounting for the low protein and relatively high globulin. In nephrosis of infancy, Ebel found the same serum protein picture as in adults.

Linder, Lundsgaard and van Slyke attempted to correlate the albumin-globulin ratio in the serum of nephritic patients with the degree of edema and proteinuria, and the clinical type of disease. In glomerulonephritis of the nephritic type, with edema, the plasma protein was uniformly low, from 3.5 to 5.5 per cent in active cases, and the ratio

was 0.8 to 0.6. The low protein content corresponded to severe albuminuria. In glomerulonephritis of the vascular type, however, the serum protein was normal qualitatively and quantitatively, except for an antemortem drop in one case. Nephrosis with edema and albuminuria was associated with low protein in all severe cases, from 3 per cent up, and a low ratio, to 0.26; with disappearance of the edema and improvement, the serum protein tended to return to normal. In nephrosclerosis and albuminuria, abnormality was not observed. The authors concluded that there was not any exact correlation between the degree of edema and protein concentration, and that, therefore, the edema was probably not the result of low serum protein and decreased osmotic pressure. They regarded two factors as responsible for the diminution of serum protein—disturbance in protein production consequent on the nature of the disease, and loss of protein in the urine.

Working on the same subject, Fahr and Swanson obtained similar results. They calculated the arithmetic means in normal subjects, finding plasma protein 7.1 per cent $\pm$ 0.5, albumin 4.5 per cent $\pm$ 0.5 and globulin 2.6 per cent $\pm$ 0.4. In glomerulonephritis, and especially in nephrosis, there was a reduction in plasma protein, the lowest value being 3.4 per cent, and a marked reduction in albumin, the globulin was normal or slightly above absolute and there was a consequent drop in the albumin-globulin quotient, ranging from 0.5 up. In three of four cases of hyperpiesis with heart failure, a diminution of albumin and of plasma protein was also observed. The authors could demonstrate an inverse correlation between the degree of edema and amount of plasma protein, especially albumin, in many cases, but concluded that a causal relation did not exist between the two. Edema was sometimes found with normal plasma, or markedly reduced protein without edema. A high protein diet in one patient with nephrosis did not cause an appreciable rise in the plasma protein. Loss of protein in the urine appeared to be an important factor in its diminution in the blood, but an additional one, probably metabolic in nature, must exist also. A conclusion was not reached as to the significance of the osmotic pressure of plasma colloids for the formation of edema, and the need indicated for measurements of osmotic pressure directly during the formation and disappearance of edema.

Stillman determined that gross changes in plasma volume did not occur in disease of the kidneys, indicating that an actual decrease of plasma protein in the body was involved, and not a condition of "hydremic plethora." Rusznyak and his associates confirmed the globulin increase in nephrosis.

Kollert and Starlinger, in their interesting work with Rohrer's method, attempted to explain the relation between albuminuria and the composition of the blood and urine. They regarded albuminuria as

the result of increased protein destruction and increased premeability of the kidney. Protein destruction is manifested by increase of the coarsely dispersed proteins in the serum globulin and especially fibrinogen, and increased excretion of urea in the urine, as in nephrosis and pneumonia. The total serum protein was low in these cases. When the fibrinogen sank below a certain level, the albuminuria disappeared. In fact, Kollert and Starlinger showed definite parallelism between the fibrinogen content of the serum, degree of albuminuria and excretion of urea. In 1924, from studying eighty cases of nephrosis and nephritis, they concluded that the degree of albuminuria had a definite relation to the composition of the serum proteins, and that high fibrinogen and globulin corresponded to severe albuminuria, and consequent decreased albumin in the serum. That albuminuria can, however, exist without change in the blood proteins was shown by the normal results in albuminuria resulting from lordosis, and nearly normal in that caused by passive congestion of the kidneys. Kollert divided the nephrosis into two types, according to observations of serum protein: the first, a necrotic process affecting the kidneys alone, with little if any change in serum protein; the second, a general metabolic disease, the lipoid nephrosis of Epstein, accompanied by the marked alteration in the protein as described by Epstein and others. In their last report in 1926, Kollert and Starlinger changed to the gravimetric method as being more accurate, and obtained the same results. They found the fibrinogen increased in all types of nephritis, but most markedly in nephrosis. The degree of proteinuria, of which one third was usually globulin, corresponded to the increase of fibrinogen and decrease of total protein in the blood. However, there was no exact correlation between variations in the latter and the clinical course in the individual nephritic patient.

Berger, in 1924, summarized the influence of disease on the serum proteins. Most local and general diseases have been found to influence the protein content to some extent and in various directions. Quantitative changes consist of a decrease, as in hydremia, inanition, edema caused by starvation, neoplasms, acute infections and nephritis, or an increase, as in loss of water through thirst, sweating, venous stasis or diarrhea; also in muscular work, in late stages of starvation, in convalescence from acute infections, in tuberculosis and following protein injections. These changes were at first attributed solely to the passage of water in and out of the vessels, so that the protein content was thought to be an accurate measure of the blood concentration, but later movements of the proteins themselves were accepted as important factors. The chief qualitative change is a shifting of the protein toward the labile or coarsely dispersed fraction, that is, an increase in globulin. This appears to be a chemical expression of almost all pathologic processes with general manifestations. Or, according to Leendertz, in

all wasting disease accompanied by tissue destruction, the labile or coarsely divided protein is increased. This can be correlated with decreased sedimentation time of the red blood cells. The relationship between changes in the serum protein and local or general injury to tissue suggests that the source of the former is in the cellular protein or close to it.

The behavior of the serum proteins during immunization is of much interest on account of the association of antibodies with the globulin fraction. The question has been repeatedly investigated, not always with uniform results. Szontagh and Wellmann first found the protein slightly increased from 7.567 to 7.820 per cent in two horses immunized to diphtheria. Butjagen confirmed this result. The globulin content was somewhat increased, according to Seng.

Hiss and Atkinson also found the globulin higher in immune than in normal horse serum, and higher in the same horse after immunization, but the increase in globulin did not correspond to the antitoxin content of the serum. Joachim's work in 1902 showed increase in globulin and no change in total protein in the serum of a horse immunized to diphtheria. It is interesting to note that the pseudoglobulin content did not change while the euglobulin increased to double its former value. The albumin decreased from 5 to 3.7 per cent Langstein and Mayer. injecting a variety of organisms into rabbits, concluded that the total protein was increased in all types of infection, and that the globulin fraction rose with the development of immunity. Moll, agreeing with them, regarded this relation as necessary. He also reached the erroneous conclusion that albumin, under proper physical and chemical conditions, changed into globulin. This possibility has since then been repeatedly affirmed and denied.

Glaessner, in 1905, was apparently the first to doubt the necessity of correlation between increase of globulin and development of immune bodies. He attributed the change in serum protein to malnutrition and other disturbances during the injections, and by using small doses and great care, was able to immunize animals without causing any increase in serum globulin. Müller confirmed this, but found the total protein slightly increased. In further experiments with diphtheria, immunization, Ledingham again found increase of the percentage of globulin, chiefly the euglobulin, in a horse with high grade antitoxic serum, and no increase in one which failed to yield good antitoxin. Gibson and Banzhaf in 1910 reported the same change, but not always corresponding to the antitoxic strength of the serum. Thus, the second highest globulin content was found in the serum of a refractory horse. They found an equal change in the two types of globulin, and called attention to the interesting fact that the protein is quickly regenerated since the value was little changed by repeated large bleedings.

Hurwitz and Meyer, in 1916, started a series of experiments on the relation between serum globulin and antibodies, using Robertson's method. At first they found that immunization of rabbits with living or killed bacteria, or with endotoxins, resulted in a marked increase of globulin, so that the ratio of albumin to globulin, normally 3.5, fell to below 1. There was, however, a lack of correspondence between the change in protein quotient and the degree of immunity developed. A year later, Hurwitz and Whipple made protein injections in dogs, producing immunity without change in the serum proteins. Intoxication resulting from intestinal obstruction was accompanied by a marked fall in the protein quotient, in one dog with a complicating peritonitis a fall to 0.2. Their conclusion was that the increase in globulin resulted from shock and intoxication, and was in no way related to the production of immune bodies. Schmidt and Schmidt also succeeded in immunizing rabbits to various proteins, without any change in the protein quotient. Meyer, Hurwitz and Taussig then immunized animals to the toxins of diphtheria, tetanus and botulism, causing an increase in globulin which corresponded rather to the degree of general reaction than to the antitoxic potency of the serum. The change appeared to be a manifestation of disturbed metabolism resulting from the toxic inoculations. Hanson found that injections of trypsin, an antigen whose antibody is known to be in the albumin fraction, did not cause a change in the protein quotient, and Clark showed the same for gelatin. Contrary to some of the former work, the quotient also remained unchanged during alternating periods of digestion and starvation.

Doerr and Berger, in 1921, injected foreign serums into animals, and obtained an increase of the globulin from 29.7 per cent of the protein to 51 per cent. The albumin underwent a corresponding decrease. Berger, using Rohrer's method, followed more closely the changes resulting from injections of foreign protein. The total protein increased (from 7 to 9 per cent), remained high for from twenty to thirty days, diminished and often underwent a second smaller rise. The globulin, after a short latent period, decreased a little, then reached a high level and remained high for from twenty to fifty days. The albumin was low during this period, but increased afterward, causing the second peak in the protein curve. Since the rise of one protein fraction was not balanced by the fall of the other, Berger did not think a change from albumin to globulin had taken place, and since the two did not vary together, obviously a true change in the protein content was involved, not merely a change in the concentration of the blood.

The work of Ruppel, Ornstein, Carl and Lasch on the serum of a horse, before and after immunization to diphtheria, revealed a slight increase in protein, marked decrease of albumin, increase of euglobulin and no change in the pseudoglobulin. They thought the change from

albumin to globulin possible in vitro under the influence of warmth, alkalinization or the electric current, and speculated as to whether it took place in the body. Löhr and Löhr also found a relative increase of globulin after injections of protein, and related it to a decrease of the sedimentation rate of the red blood cells. In 1925, Sordelli and Mazzocco immunized horses to diphtheria and using the Kjeldahl nitrogen method, reported increased total protein, decreased albumin and increased globulin, chiefly the euglobulin fraction. The antitoxic potency of the serum corresponded neither to the increase in protein nor to that in globulin. Much the same result was obtained by Bächer and Kosian. Although there was a constant increase in total protein and in globulin, especially the pseudoglobulin fraction, during diphtheria immunization, this change toward greater lability could not be correlated with the degree of antibody formation. It seemed rather to depend on the length of the immunizing period, degree of general reaction and number of bleedings. It did not occur during immunization to cholera, dysentery, tetanus and other infections. They also found an increase in the labile protein with aging of the serum (three years).

Reymann reviewed the literature on serum protein during immunization up to 1924, and in his experiments confirmed the general opinion that total protein and globulin are increased and albumin decreased. The average changes found in twenty-four horses immunized to diphtheria were: protein from 7.23 to 8.57 per cent; globulin from 4.17 to 6.27 per cent, and albumin from 3.01 to 2.25 per cent. The increase in globulin involved chiefly the pseudoglobulin and the fraction soluble in sodium chloride. Investigating the relationship between antibody formation and globulin increase, Reymann also concluded that a parallelism between the two did not exist. He suggested that the normal amount of globulin in the serum was not sufficient to adsorb all the newly formed antitoxin.

An interesting contribution to the question was made by Howe and his associates. He found that the blood of new-born calves did not contain euglobulin or pseudoglobulin I, while colostrum was rich in these proteins. A large proportion of the agglutinins for *Bacillus abortus* was precipitated with the euglobulin, and the appearance of the missing fractions in the calves' blood following ingestion of colostrum was associated with absorption of these agglutinins. Along the same line, Lewis and Wells found that infants, like the calves, had practically no euglobulin in the blood at birth. This protein was acquired first from the mother's colostrum, with its high globulin and corresponding antibody content. Furthermore, the globulin of the milk and serum were shown to be the same, while the albumins of the two fluids differed markedly.

Wichels (1926) investigated the difference in reaction to antigenic and nonantigenic substances and on the part of normal and allergic

persons. From a review of the literature he concluded that in infection or immunization a regular shift occurs in the serum protein, with first a fibrinogen peak, then a globulin peak and finally an albumin peak. He found a marked difference in the reaction of normal and allergic persons (patients with chronic infections) to the injection either of antigens or of nonantigens, in that the former showed an increase in serum albumin, and the latter one in serum globulin. The shift began twelve hours after injection, reaching its height in from twenty-four to forty-eight hours. This difference in response is regarded as evidence for the separate formation and nature of the two proteins, and can be explained on the assumption that globulin is formed in the cells of the reticulo-endothelial system, and albumin in the other body tissues. The stimulus of the injection in a normal person calls forth a general reaction, with an increasing formation of albumin, while in an allergic person the reaction is chiefly on the part of the reticulo-endothelial system, leading to an increased output of globulin.

SUMMARY OF RESULTS REPORTED IN THE LITERATURE

I. Methods of Determining Concentration of Serum Proteins.

1. Precipitation of the protein and its fractions with acids, alcohol, or salts, with
   (*a*) direct weighing of the precipitate, or
   (*b*) determination of its nitrogen content chemically.
2. The gas volumetric method of Jolles.
3. Refractometric methods.
4. Colorimetric methods.
5. Refractoviscosimetric method of Nägeli and Rohrer.
6. Nephelometric method.
7. Interferometric method.
8. Modified salting-out and chemical methods of Cullen and van Slyke, and Howe.
9. Leendertz method for serum lability.

The various chemical methods seem to give the most accurate absolute results. However, the physical measurements have the advantages of greater simplicity and of requiring less serum, and appear to be accurate enough for comparative observations.

II Physiologic Variations.

The serum proteins differ with the species of animal. In infancy, both in animals and man, the total protein, and especially the globulin fraction, are lower than in adults. Food, liquid, exercise and sleep exert only slight influences. In menstruation the protein is below normal with the globulin relatively increased. In pregnancy, decreased protein

has been most frequently reported, with the globulin relatively increased, but the opposite result has been obtained by some workers. The injection of salt or sugar solution is followed by a diminution of the serum protein. The results in starvation vary. Usually, a decrease in protein is reported, involving the albumin more than the globulin, and the albumin is restored more rapidly on an adequate diet. Repeated bleeding reduces the protein content. In starving animals, the globulin is restored most rapidly.

III. Variations in Disease.

1. In the acute infectious diseases the protein content of the serum is reduced, while the globulin fraction is increased.
2. In active tuberculosis the protein is usually increased, but in patients with marked cachexia it may be decreased. The globulin is always increased, the degree roughly corresponding to the severity of the disease.
3. In syphilis the globulin fraction is increased.
4. In the diseases of infancy, severe atrophy or malnutrition is accompanied by low serum protein, and diarrhea is accompanied by high protein content from loss of fluids, except that in intoxication, with loss of tissue as well as of fluids, the protein is again low.
5. In both pernicious and secondary anemias the serum protein is reduced.
6. Most diseases of the liver are accompanied by increased globulin and decreased total protein.
7. In diabetes the protein is usually low, but it may appear to be high from loss of water.
8. In malignancy most reports indicate diminished protein, with relatively increased globulin, but an increase of protein has been reported by some investigators.
9. Following surgical procedures the globulin proportion has been found to be increased.
10. In cardiac disease with edema the serum protein is reported both above and below normal.
11. In glomerular and parenchymatous nephritis, the protein is usually reduced, with a high proportion of globulin. This change is especially marked in chronic nephrosis. In nephrosclerosis, and in glomerulonephritis of the vascular type, according to some, the protein is normal, unless cardiac decompensation is present also.

Contrasting renal and cardiac edema, investigators agree that in the former low values for the serum proteins are found, but they disagree in the latter condition, some finding the protein slightly low, others

normal or slightly above normal. At all events, there seems to be a difference between the two types of edema.

It seems generally agreed that a causal relation does not exist between diminished plasma protein and edema. Close correlation has been shown, however, between the degree of albuminuria, decrease in serum protein and increase in fibrinogen. The low protein in nephritis has been explained on the basis of loss in the urine along with some other metabolic factor, probably a disturbance in the formation of protein.

IV. Serum Proteins in Immunity.

The change generally found during immunization is an increase in total protein and in the proportion of globulin. It has been shown, however, that immunity can be developed without this change, and that the shift in the protein does not always correspond to the degree of immunity developed.

The most general alteration of the serum proteins in disease and immunization is a shift in favor of the labile globulin fraction.

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Notes and News

American Society of Clinical Pathologists.—The sixth annual meeting was held in Washington, May 13, 14 and 16, 1927. During the first two days scientific papers were presented and discussed, and the entire third day was given over to the discussion of questions of business and organization. Fifteen clinical pathologists were admitted to membership. Officers for 1927-1928 were elected as follows: president, A. H. Sanford, Rochester, Minn.; president-elect, Frank W. Hartman, Detroit; vice president, H. J. Nichols, Quarry Heights, Panama; secretary-treasurer, Ward Burdick, Denver.

University News, Promotions, Resignations and Appointments.—Clyde L. Cummer has resigned as associate professor of clinical pathology in the medical school of Western Reserve University, Cleveland.

At the celebration of the five hundredth anniversary of the founding of the University of Louvain, the honorary degree of doctor of medicine was conferred on James B. Murphy of the Rockefeller Institute for Medical Research.

Howard T. Karsner, professor of pathology in the school of medicine of Western Reserve University, has been appointed chairman of the division of medical sciences of the National Research Council, Washington, D. C., for one year beginning Sept. 16, 1927.

George Caldwell, professor of pathology, Baylor College of Medicine, Dallas, Texas, and his wife, Janet A. Caldwell, head of the laboratory and research department at the college, have accepted positions to manage the new hospital and clinic under construction at Mineral Wells by the Crazy Water Hotel Company.

Ralph Paterson Smith has been appointed professor of pathology in Dalhousie University and pathologist to the Victoria General Hospital in succession to Albert G. Nicholls, resigned.

Henry Hartman, professor of pathology in the University of Texas, has accepted also the deanship in the school of medicine.

Lewis C. Pusch has been appointed associate in pathology in the Medical College of Virginia.

Glenn C. Carbaugh has been appointed chief deputy coroner of Kansas City, succeeding Charles S. Nelson, who resigned to do postgraduate work in Europe.

W. C. Johnson, associate professor in the department of pathology in the College of Physicians and Surgeons of Columbia University, and pathologist for the Sloane Hospital, New York, has been appointed during his sabbatical leave of absence from Columbia University, professor and head of the department of pathology in the University of Colorado Medical School in Denver.

David P. Seecoff, until recently pathologist for the Montifiore Hospital, New York, has been appointed associate professor of pathology in the University of Colorado Medical School in Denver.

Frank B. Mallory, pathologist to Boston City Hospital, has accepted a professorship of pathology in Harvard Medical School.

Section of Pathology and Bacteriology at 1927 Meeting of British Medical Association.—The following subjects were discussed: Growth in Its Pathological Relations, by Archibald Leitch, Robert Muir, Shaw Dunn, M. J. Stewart,

E. H. Kettle and J. Lorrain Smith; Immunity, by R. A. O'Brien, C. H. Browning, Robert Muir, E. L. Opie, W. F. Harvey, D. C. Matheson, Hedley Wright, W. H. Andrews and T. J. Mackie; Comparative Medicine, by Basil Buxton, Andrew Balfour, W. H. Andrews, J. Lorrain Smith, C. H. Browning and others.

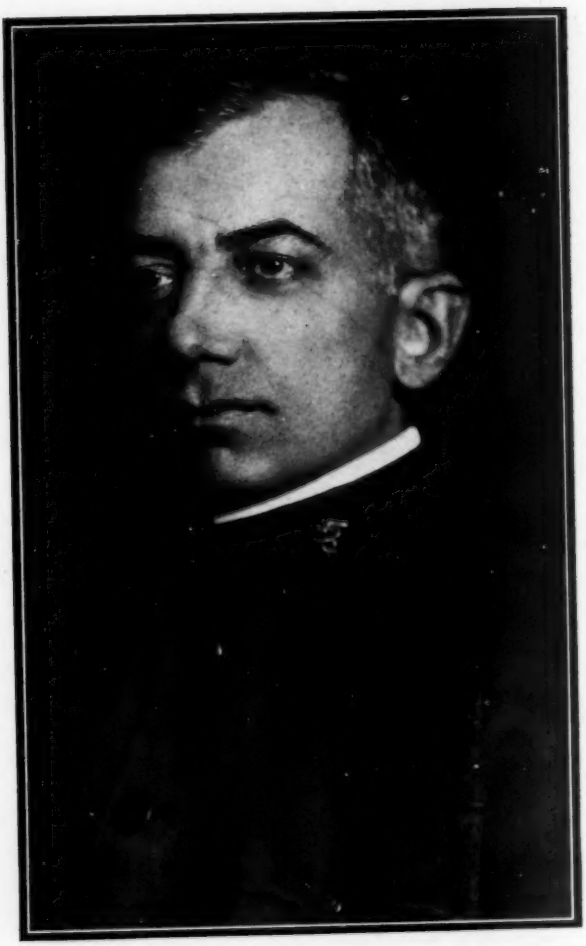
Section of Forensic Medicine at 1927 Meeting of British Medical Association.—The subjects for discussion were alcohol and the motorist, and the teaching of forensic medicine. It was emphasized that in forensic medicine courses of instruction analogous to those given in public health are needed for the practitioner; also that the creation of medicolegal centers should be urged.

Death of Henry Harvey Littlejohn.—Henry Harvey Littlejohn, regius professor of forensic medicine in the University of Edinburgh and author of a textbook on his specialty, has died.

Medical Fellowships of the National Research Council.—Claus W. Jungeblut, on the expiration of his fellowship under the National Research Council, has accepted an assistant professorship of bacteriology in Stanford University. Hobart A. Reimann, recently working with Professor Ghon in Prague under a fellowship of the National Research Council in pathology, has been appointed assistant professor of medicine in the Peking Union Medical College. At at recent meeting of the Medical Fellowship Board, Louis H. Jorstad was awarded a fellowship in pathology and Oran I. Cutler was reappointed as fellow to work in pathology at the University of Chicago. In addition, the following appointments were made: W. C. Austin, physiology and organic chemistry; Arthur L. Caldwell, chemistry and physics leading to internal medicine; Milton R. Earl, anatomy; Edgar R. Fintcher, neurosurgery; Ethel D. Simpson, physiology; Richard W. Whitehead, pharmacology, and Harold D. Wolff, neurology.

Nobel Prize to Fibiger.—Johannes Fibiger, professor of pathologic anatomy in the University of Copenhagen, has been awarded a Nobel Prize in medicine for his work on carcinoma of the stomach of rats following infestation with *Spiroptera neoplastica.*

Death of C. E. Simon.—Charles Edmund Simon, professor of filtrable viruses in the John Hopkins University School of Hygiene and Public Health has died. He was born in 1866. In 1907, he established the first clinical laboratory in Baltimore. He was the managing editor of the *American Journal of Hygiene* and author of "Infection and Immunity" and other books.



HENRY JAMES NICHOLS, M.D.

Obituary

HENRY JAMES NICHOLS, M.D.

LIEUTENANT-COLONEL, MEDICAL CORPS, U. S. ARMY

1877-1927

The tragic death of Lieut.-Col. Henry J. Nichols, Medical Corps, U. S. Army, at Ancon Hospital, Panama, on Sept. 3, 1927, deprived the Army of a loyal and distinguished officer and scientific medicine of an enthusiastic and devoted worker.

Colonel Nichols was born, May 21, 1877, in Milwaukee. He received the degrees of bachelor of arts and master of arts from Yale University, in 1899 and 1901, respectively, and was a member of the Phi Beta Kappa fraternity. He studied medicine at the University of Pennsylvania and was graduated as doctor of medicine in 1904. During the following year, he entered the Medical Corps of the U. S. Army, and in 1906 was graduated from the Army Medical School. On July 6 of that year, he was commissioned as first lieutenant in the Medical Corps; he was made captain in 1909, major in 1916 and lieutenant-colonel in 1926. He held the rank of temporary lieutenant-colonel during the World War.

Colonel Nichols was an active research worker in bacteriology, serology and preventive medicine, and held many important positions in the laboratory services of the army. His published contributions to medical literature cover a wide range of subjects. He was associated with the pioneers in the production of triple typhoid vaccine and in the use of arsphenamine in this country, while his studies of experimental syphilis in rabbits, of human typhoid carriers and of many other subjects have been of great practical value.

In 1922, he published a useful work entitled, "Carriers in Infectious Diseases."

Colonel Nichols was a member of the U. S. Army Board for the Study of Tropical Diseases in the Philippines, from 1907 to 1910, and had charge of the Mary J. Johnson Cholera Hospital in the Philippine Islands in 1908. At different times he was in charge of various large department or corps area laboratories. From 1910 to 1914, he was associate professor of clinical pathology and bacteriology at the Army Medical School.

In 1920 he returned to the Army Medical School and in 1923, became director of laboratories and of the department of preventive medicine and hygiene. He went into foreign service in the Canal Zone in 1926, as medical inspector of the Panama department of the United States Army, and held this important position at the time of his death.

Colonel Nichols was an enthusiastic supporter of a large number of scientific societies, including the American Society of Tropical Medicine, of which he was a charter member and past president; the Royal Society of Tropical Medicine and Hygiene, England; the American Association for the Advancement of Science; the Society of American Bacteriologists; the American Society of Clinical Pathologists, and the American Society of Experimental Pathologists. He was a Fellow of the American Medical Association; of the American Public Health Association, and of the American College of Surgeons; and a member of the medical division of the National Research Council. Colonel Nichols was a founder of the *American Journal of Tropical Medicine*, which he edited until his departure for foreign duty in 1926. Since that time he had been the associate editor.

A host of friends deeply regret his premature death.

Abstracts from Current Literature

Pathologic Physiology

THE RELATION OF MATERNAL DIET TO HEMORRHAGE IN THE NEW-BORN. C. U. MOORE and J. L. BRODIE, Am. J. Dis. Child. **34**:53, 1927.

A case is reported in which the mother's prenatal diet was markedly deficient in water soluble vitamin B; delivery was accompanied by excessive hemorrhage and death of the child occurred five days after birth, bleeding having been apparent for two days prior to death. The conditions observed at autopsy resembled those found in experimentally produced avitaminosis in animals.

RUTH E. TAYLOR.

SUDDEN TRANSITORY REDUCTION IN THE VISCOSITY OF THE BLOOD AS A CAUSE OF THE FALL IN BLOOD PRESSURE IN "SHOCK." R. A. WAUD, Am. J. Physiol. **81**:160, 1927.

The author reports the results of a series of experiments in which viscosity determinations were made of the blood before and after the injection of peptone, histamine or antigen. From these experiments, he deduces that the fall in blood pressure in anaphylactic shock and similar conditions is due to a sudden lowering of the viscosity of the blood. This permits readier passage of the blood through the small arterioles, with increase of blood pressure and volume in the capillaries. Following the decreased viscosity there is a period of marked increase, and the author suggests that an extension of this to muscle plasma may be associated with bronchial muscular spasm. As a factor in the production of edema in shock, he considers as probable a reduction of viscosity in the limiting membrane of the endothelial cells of the capillaries.

H. E. EGGERS.

THE RÔLE OF THE GALLBLADDER IN THE REGULATION OF THE FLOW OF BILE. G. E. BURGET, Am. J. Physiol. **81**:422, 1927.

Observations were made of pressure changes in lightly anesthetized dogs and cats by means of small rubber balloons inserted into the gallbladders, and in some cases into the duodenum as well. In 75 per cent of the dogs, rhythmic changes were observed, at the rate of from two to three per minute. There was no evidence of a relationship between these and duodenal peristalsis, even after the intravenous administration of eserine. They were affected to a slight degree by drugs acting on the nerve supply of the gallbladder, and barium chloride, acting directly on the musculature, gave definite augmentation. When the gallbladder was traumatized or its circulation injured, the organ became edematous; in this case the tonic contractions failed to appear, and there was a gradual increase of pressure simulating the effect of a slow contracture. Contractions that might be considered of major importance in causing flow of bile were not observed; the writer considers that this is determined by the tonicity and peristalsis of the duodenum, with the elasticity of the wall of the gallbladder when under tension as one auxiliary factor and intra-abdominal pressure as another. For instance, a fat meal does not induce contraction of the gallbladder, but it temporarily lowers the tonus of the small intestine.

H. E. EGGERS.

THE RELATION OF TISSUE-ACIDITY AND BLOOD-ACIDITY TO VOLUME-FLOW OF BLOOD AS ILLUSTRATED BY HEMORRHAGE AND REINJECTION. A. B. HERTZMAN and R. GESELL, Am. J. Physiol. **81**:563, 1927.

The effects of hemorrhage and reinjection on blood acidity were studied in dogs by means of the manganese dioxide and hydrogen electrodes. It

was found that hemorrhage increased the alkalinity of the arterial blood and the acidity of the venous blood. At the same time there was decreased consumption of oxygen, and increased pulmonary ventilation. The reverse effects were obtained on reinjection. Constant artificial ventilation did not affect the directional character of these blood changes during hemorrhage and reinjection.

The authors conclude that the increased alkalinity of the blood during hemorrhage is due not to increased tidal air alone, but to the amount of pulmonary flow as well, thus supporting the idea of the importance of volume flow of blood in the maintenance of normal acid-base equilibrium. That this is of especial importance in the pulmonary circuit was indicated by the fact that during constant pulmonary ventilation hyperacid venous blood leaves the lung distinctly more alkaline than normal.

H. E. Eggers.

Observations on the Rôle of Tissue in Maintaining Acid-Base Equilibrium of Blood. I. Effect of Isolated Muscle Tissue. L. N. Katz and M. G. Banus, Am. J. Physiol. **81**:628, 1927.

The authors describe an apparatus for perfusing isolated organs with normal or modified blood, under conditions of adequate control of pressure, flow, temperature and carbon dioxide tension. A method for the isolation of the gastrocnemius muscle of the dog, and for its perfusion under conditions as closely as possible approximating the physiologic is described also. They give their reasons for assuming that the results obtained in these conditions are applicable to conditions in the body, for a perfusion period of not over three hours.

To ascertain the availibility of the buffering materials in the muscle, as a reserve for the blood, the gastrocnemius was perfused with blood acidified within physiologic limits by the addition of dilute hydrochloric acid.

Making p_H determinations by a modification of the electrometric method, the changes in p_H carbon dioxide combining power and chloride content were determined at constant carbon dioxide tensions. The results obtained during the perfusions indicated that no measurable exchange of chloride or alkaline radicals occurred between blood and muscle, following perfusion with the acidified blood, so that the acid-base balance of the blood was unchanged. With constant carbon dioxide tension, the muscle did not increase the buffering power of the blood to a measurable degree. The authors explain this on the basis, under the conditions of the experiment, of a lack of permeability of the muscle tissue for the buffering substances.

H. E. Eggers.

Observations on the Rôle of Tissues in Maintaining Acid-Base Equilibrium of the Blood. II. Effect of Hind-Leg Preparation. M. G. Banus and L. N. Katz, Am. J. Physiol. **81**:644, 1927.

Using the isolated hind leg of the dog under the technic of the foregoing article, the authors observed an increase of p_H and carbon dioxide combining power of the acidified blood following perfusion. No alteration was observed in the concentration of the chlorine ion of the blood. Accordingly, some of the tissues of the leg would appear to increase the buffering capacity of the blood perfused through them. From their previous experiments on isolated muscle, that would not appear to be concerned in the process. The nature of the tissues concerned and the exact nature of the process are still unknown.

H. E. Eggers.

The Relation of Volume, Hydrogen Ion Concentration and Buffer Capacity of the Test Meal to Gastric Contents. W. A. Standish, G. R. Cowgirl and A. T. Shohl, Am. J. Physiol. **81**:696, 1927.

Using two dogs with gastric fistulas, the authors found that the amount of gastric juice secreted is proportional to the volume and concentration of the

test meal, so as to increase the p_H from between 4.1 to 3.9 for all meals. Once established, the p_H of the contents of the stomach tends to remain constant until the end of digestion. With concentrated meals and those of large volume, more time is required for digestion than for dilute or small meals, so that the motility of the stomach varies with the volume and concentration of its contents. As regards buffer capacity, this stays fairly constant after an initial increase. The beginning of digestion, when the contents of the stomach are large, is associated with a large buffer capacity; small buffer capacity with small volume of contents occurs at the end of digestion. Concentration exerts an important and quantitatively measurable effect both on secretion and on motility.

H. E. Eggers.

Renal Excretion with Special Reference to Ambard's Laws. B. S. Walker and A. W. Rowe, Am. J. Physiol. **81**:738, 1927.

The authors discuss the several so-called "laws" of kidney excretion, and analyze their mathematical formulation. Also, they have carried on experiments to test the validity of these so-called laws. The first law of Ambard was found to be correct within rather narrow limits — at best a rough approximation to the expression of actual relations. The second law was found to be completely invalid. In spite of its dubious basis, the third law of Ambard — a combination of the first two — was found to express approximately the known conditions of the function of the kidney. The authors believe the explanation of this apparent paradox may be reached through statistical analysis of available data.

H. E. Eggers.

The Relation of Blood to Urine Urea. B. S. Walker and A. W. Rowe, Am. J. Physiol. **81**:755, 1927.

As a result of the statistical analysis of their own data and those of other investigators, the authors find that the parabolic relationship between blood and urine urea, as proposed by Ambard, is more nearly in accordance with observed fact than is the rectilinear relationship as proposed by Adolph, and they give the exponential equation of the curve of elimination. For the purposes of simplification, they establish certain limits to the constants of Ambard's first equation, and define three zones of normalcy, abnormalcy and an intermediate uncertain area. They have based a simple method for testing functional capacity on this classification. As a result of the study of the influence of volume of urine on the excretion of urea, they believe that there is a relationship between them which is as yet undefined.

H. E. Eggers.

Hypertension in Pregnancy. E. J. Stieglitz, Arch. Int. Med. **39**:465, 1927.

According to Stieglitz, hypocalcemia is not of major etiologic significance in arterial hypertension in pregnancy, despite the fact that in such cases the relationship should be most conspicuous. During the final month of pregnancy, a gradual rise in arterial tension is associated with a moderate hypocalcemia. Immediately after parturition a fall in blood pressure occurs, with a corresponding rise in the blood calcium concentration. Coincident and probably associated with the onset of lactation a secondary elevation in arterial tension occurs, with a corresponding and equally transient hypocalcemia. The latter phenomenon permits of physiologic interpretation.

S. A. Levinson.

Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women. E. E. Osgood and H. D. Haskins, Arch. Int. Med. **39**:643, 1927.

The actual average red cell count in 100 women from 18 to 30 years of age was 4.8 million, 90 per cent of the cases falling between 4.3 and 5.3 million.

The average total hemoglobin per hundred cubic centimeters of blood in young women is 13.7 Gm., with 90 per cent of the results falling between 12 and 15.5 Gm. In men, the average was 15.8 Gm., and 90 per cent of the results fell between 14 and 18 Gm. The average hemoglobin coefficient in young women is 14.3 Gm. and in men, 14.7 Gm. These are the figures that should be taken as 100 per cent hemoglobin in calculating color indexes of young adults. The total volume of packed red cells per hundred cubic centimeters of blood averages 41 cc. in women (90 per cent between 37 and 45) and 45 cc. in men (90 per cent between 40 and 50). The average volume coefficient in women is 42.8 cc., and in men, 41 cc., provided the authors' technic is used. These are the figures that should be used as 100 per cent in calculating volume indexes. The various indexes (color, volume and saturation) will average 1 in normal young adults if they are properly calculated and are based on accurate estimations of cells, hemoglobin and cell volume. About 90 per cent of the results will fall between 0.9 and 1.1.

S. A. LEVINSON.

STUDIES IN ACROMEGALY. G. CUSHING and L. M. DAVIDOFF, Arch. Int. Med. **39**:673, 1927.

Acromegaly is a disease which bears the same relation to pituitary insufficiency (hypopituitarism) that exophthalmic goiter bears to myxedema (hypothyroidism). In other words, it is an expression of hyperpituitarism just as exophthalmic goiter is of hyperthyroidism. Acromegaly is often accompanied by an elevated basal metabolic rate, and the reverse condition of hypopituitarism, by a subnormal rate. Acromegaly, furthermore, is often accompanied by a palpably enlarged thyroid and by symptoms suggesting thyrotoxicosis to which the increased basal metabolic rate has generally been ascribed. Occasionally, patients with acromegaly have been operated on for goiter under the assumption that the symptoms were due to primary hyperthyroidism. The gland in three such cases has been found to show merely colloid changes of adenomatous type without the expected evidences of toxicity. Nevertheless, thyroidectomy has served to lower the metabolic rate, and a compound solution of iodine has also been shown capable of lowering it. On the other hand, operations on the chromophilic hypophysial adenoma itself in cases of acromegaly in which the basal metabolism is elevated, even in the absence of a palpably enlarged thyroid, are followed by a fall in the metabolic rate almost as uniformly and strikingly as are the operations on the thyroid in exophthalmic goiter. The chromophilic cells of the anterior lobe of the pituitary body secrete a substance which not only contains the hormone of growth, but which is capable of raising the basal metabolic rate. Whether the hypophysial principle under these circumstances acts as a stimulus to metabolism directly on the tissues or only through the intermediation of the thyroid cannot as yet be positively stated, although there are reasons to believe that it may act independently. In either event, whether the effect is primary or secondary, the elevation of the metabolic rate may properly be ascribed to the hyperpituitarism.

S. A. LEVINSON.

THE PATHOLOGY OF METABOLISM IN OBESITY. H. C. HAGEDORN, C. HOLTEN and A. HECHT JOHANSEN, Arch. Int. Med. **40**:30, 1927.

A number of normal and obese persons have been examined by determining their respiratory quotients by means of a self-recording apparatus after they had taken a diet for two days that consisted chiefly of carbohydrates. By this method a real difference between the mean respiratory quotient in obese and in normal persons has been found, the respiratory quotient in obese patients being lower than that in normal persons. The results confirm the hypothesis that obesity is due to a qualitative anomaly in metabolism, i. e., an abnormally increased transformation of carbohydrate into fat. It has been shown that a relation is found between the percentage overweight and the respiratory quotient

in obese subjects, patients with great overweight having a particularly low respiratory quotient, while the patients with less overweight have a respiratory quotient which is nearer or within the normal zone. AUTHORS' SUMMARY.

PAROXYSMAL CYANOSIS ASSOCIATED WITH BILATERAL THROMBOSIS OF THE SUPRARENAL VEINS. EDWIN F. HIRSCH and J. A. CAPPS, Arch. Int. Med. **40**:112, 1927.

In a patient with bilateral thrombosis of the suprarenal veins and acute degeneration of the suprarenals, there was in addition to asthenia, low blood pressure, gastro-intestinal disturbances and syncope, sudden attacks of extreme cyanosis with dyspnea and unconsciousness. It is suggested that the suprarenals may play a part in the utilization of oxygen by the tissues.

THE OVARIAN FOLLICULAR HORMONE IN THE BLOOD OF THE PREGNANT WOMAN. MARGARET G. SMITH, Bull. Johns Hopkins Hosp. **41**:62, 1927.

The concentration of a substance, identical in its biologic property with the ovarian follicular hormone, increased in the blood of pregnant women from the onset to the termination of pregnancy. It has always been found in the same concentration during and shortly before labor, and its concentration at this time is greater than that found at any other time. There is an immediate rapid disappearance of this substance from the blood following delivery. It can be demonstrated in the urine before and following labor. The amount found in the placenta per gram of weight is approximately twice that found in the blood per cubic centimeter. The concentration in the maternal blood during labor and in the blood from the cord is the same. AUTHOR'S SUMMARY.

A STUDY OF EXPERIMENTAL HEAT-STROKE. W. W. HALL and E. G. WAKEFIELD, J. A. M. A. **88**:177, 1927.

The important acute pathologic change in major heat-stroke, other than that due to the effect of high temperatures per se on the tissues, is a massive increase in lactic acid, with acidosis.

PAROXYSMAL HYPERTENSION. CHARLES H. MAYO, J. A. M. A. **89**:1047, 1927.

An instance of paroxysmal hypertension is reported in which removal of a retroperitoneal malignant blastoma was followed by disappearance of all symptoms and marked improvement in the general health. Four somewhat similar cases from the literature are mentioned. In one case there was an infiltrating nasopharyngeal carcinoma; in one, a mediastinal lymphosarcoma; in one, a tumor similar to that reported in situation as well as in structure; while in the fourth case the cause was not determined.

TOXICITY OF ZINC. V. G. HELLER and A. D. BURKE, J. Biol. Chem. **74**:85, 1927.

Zinc added to a normal ration, either as pure zinc dust, zinc oxide or as zinc salts, in amounts exceeding those found in contaminated foods, did not interfere with the growth, reproduction and normal functions of three generations of rats. Pathologic changes were not found in the organs, nor was there any perceptible increase in their ash content. Zinc is found normally in the internal organs of rats fed growing rations. It is excreted primarily through the feces.

ARTHUR LOCKE.

FORMATION OF LACTIC ACID IN THE BODY AFTER SEVERE HEMORRHAGE. C. RIEGEL, J. Biol. Chem. **74**:123, 1927.

The concentration of lactic acid in the blood is increased following severe hemorrhage, the amount and duration of the increase depending on the extent of hemorrhage.

ARTHUR LOCKE.

THE BLOOD PEPTIDE NITROGEN IN ARTERIAL HYPERTENSION. H. JACKSON, JR., D. W. SHERWOOD and O. J. MOORE, J. Biol. Chem. **74**:231, 1927.

The blood peptide nitrogen does not rise sufficiently in hypertension to be of etiologic importance.

ARTHUR LOCKE.

EFFECT OF ANTIRACHITIC VITAMIN ON THE PHOSPHORUS, CALCIUM AND p_H IN THE INTESTINAL TRACT. L. YODER, J. Biol. Chem. **74**:321, 1927.

Both irradiation and the administration of cod liver oil produce a lowering of the p_H in the intestinal tract of rats on a rachitic ration. This decrease in p_H may be responsible for the associated, increased utilization of calcium and phosphorus.

ARTHUR LOCKE.

GLYCOLYSIS IN LEUCEMIC BLOOD. H. L. SCHMITZ and E. C. GLOVER, J. Biol. Chem. **74**:761, 1927.

The rate of glycolysis in normal blood, as determined from the study of ten normal persons, varies approximately from between 15 to 23 mg. per hundred cubic centimeters of blood an hour. The initial concentration of dextrose, within a range of from 60 to 250 mg. per hundred cubic centimeters, does not affect the rate of glycolysis in normal or leukemic blood. In chronic myelogenous leukemia, the rate of blood glycolysis is more rapid than normal, except in an aleukocythemic stage. It may be as rapid as 84 mg. per hundred cubic centimeters an hour. The number of white blood cells and the rate of glycolysis tend to run parallel. The degree of immaturity of the white blood cells and the rate of glycolysis also tend to be parallel. In chronic lymphatic leukemia, the rate of blood glycolysis is seldom more rapid than normal. But when the lymphocytes are immature, the rate may be slightly rapid. Potassium cyanide, in a concentration of thousandth normal, causes a marked increase in the rate of blood glycolysis in myelogenous leukemia; in one case the rate was more than doubled. It causes a less definite increase in the rate of glycolysis in lymphatic leukemia blood, and has little effect on the rate in normal blood.

AUTHORS' SUMMARY.

CELL RESPIRATION STUDIES. BLAKE C. WILBUR, GENEVA A. DALAND and JOHN COHEN, J. Exper. Med. **46**:43, 1927. GENEVA A. DALAND and RAPHAEL ISAACS, ibid. **46**:43, 1927.

A microspirometer for the continuous study of the absorption of oxygen by living cells is described. The blood of patients with chronic myelogenous leukemia used oxygen longer in the spirometer than did the blood of normal persons, and the hemoglobin of leukemic blood was desaturated even when exposed to air. Immature leukocytes in cases of chronic myelogenous leukemia absorbed oxygen slower than the mature cells; the immature leukocytes resemble malignant cells in this respect.

BLOOD PRESSURE IN THE RABBIT AND ATHEROSCLEROSIS. R. DOMINGUEZ, J. Exper. Med. **46**:443, 1927.

Fluctuations in systolic blood pressure beyond the normal range are not necessary for producing atherosclerosis of the aorta in rabbits. Atherosclerosis from feeding egg yolk is not associated with abnormal elevation of blood pressure.

MUSCLE CONTRACTION IN ANAPHYLAXIS. ARTHUR ISAAC KENDALL, HARRY L. ALEXANDER and JANET A. HOLMES, J. Infect. Dis. **41**:137, 1927.

The observations presented herewith seem to demonstrate three distinct, but related, facts: formaldehyde, in suitable small concentrations prevents a sensitized smooth muscle from contracting on contact with its homologous

antigen; formaldehyde, in suitable small concentrations relaxes anaphylactic contractions induced in sensitized smooth muscle; and a strip of sensitized muscle exposed under proper conditions to formaldehyde and then to the homologous antigen will not respond with a contraction on subsequent contact with the homologous antigen. This would seem to indicate that the muscle has been desensitized.

AUTHORS' SUMMARY.

THE PHYSIOLOGIC ACTION OF HISTAMINE APPLIED DIRECTLY TO THE MUCOSA OF THE ISOLATED SURVIVING INTESTINE OF THE GUINEA-PIG. ARTHUR ISAAC KENDALL and PHILIP LEONARD VARNEY, J. Infect. Dis. **41**:143, 1927.

Neutral histamine solutions, applied directly to the mucosa of isolated surviving intestinal strips, usually induce slow but progressive contractions. These contractions usually become apparent after a latent period of from thirty to sixty seconds. Neutral histamine solutions applied to the serous surface of intestinal strips, on the contrary, induce rapid and abrupt contractions. Acid histamine solutions applied to the mucosa of intestinal strips either fail to induce contractions, or incite very slow and limited contractions.

The addition of weak alkali to acid histamine solutions in contact with the mucosa of isolated intestinal strips tends to accentuate both the rate and height of contractions.

The intestines taken from young guinea-pigs are in general somewhat more responsive to neutral histamine solutions applied to the mucosa than the intestines of older guinea-pigs.

The experimental evidence presented herewith points to a definite but slow absorption of histamine from the lumen of the intestines through the mucosa. Histamine thus absorbed from the intestinal lumen in the living animal is probably removed through the blood stream as fast as it is absorbed under normal conditions.

Suitable aldehyde solutions prevent or relax histamine contractions induced in isolated, surviving intestinal strips, depending on whether these aldehydes are applied before or after the introduction of the amine.

AUTHORS' SUMMARY.

ESTIMATION OF BLOOD VOLUME IN DISEASES. C. CIPRIANI and G. DOMINICI, Arch. per le sc. med. **49**:158, 1927.

In well nourished subjects, the blood volume increases slightly, but it is below normal if referred to the body weight. The opposite is the case in undernourished people. The blood volume (congo red method) was normal in diseases of the heart in which compensation occurred. It increased in cases of compensation, the increase affecting the blood corpuscles. If edemas developed, the blood volume decreased as a rule. Hypoglobulia and compensating hyperplasmia were found. Blood and plasma volume was augmented in diseases of the liver, but the increase was not parallel with the gravity of the disease. In diseases of the kidneys, the total blood volume was within normal limits (hypoglobulia with hyperplasmia). The blood volume was normal in patients with hypertension; because of loss of weight, it was relatively increased in tuberculous patients (hypoglobulia and hyperplasmia); only in grave cachexia, especially in cancer, was it notably diminished. The blood volume (plasma) increased in diabetes insipidus during the action of pituitary extract.

K. SCHULHOF.

INDICATORS IN STUDY OF REACTION OF HOMOPLASTIC GRAFTS OF SKIN. S. MILONE, Arch. per le sc. med. **49**:193, 1927.

Milone injected rats with phenol red according to Peyton Rous' technic of observations on autoplastic grafts. Homoplastic transplants of skin, which practically never take, reacted in a similar way: there was a local acidosis for

above five days (yellow-orange color), and then, sooner or later, an alkaline shifting. Death of the implanted parts occurred in some rats in the acid phase, in others in the alkaline phase. Milone also attempted to find out whether there are any differences in the reaction of the tissues in rats living in the so-called dysharmonic parabiosis, which entails desiccation and the death of one partner, while the other thrives (Morpurgo). The coloration of both rats was equal.

K. Schulhof.

Clinical and Experimental Contribution on Glycogenetic Function of the Liver in Partial Biliary Stasis. A. Brugi, Arch. per le sc. med. **49**:433, 1927.

Biliary stasis induced by incomplete constriction of the bile duct in rabbits did not have much effect on the glycemia curve after injection of dextrose. Clinically, similar observations have been made unless the stasis was of long duration (over a month). The progressive alteration of the liver cells entails a disturbance of the carbohydrate metabolism.

K. Schulhof.

Vital Capacity in Various Postures. H. Bockemühl, Beitr. z. Klin. d.Tuberk. **65**:723, 1927.

Seventy-four men, women and children who did not suffer from pulmonary disease were examined for their vital capacity in different postures. The average values were as follows: standing, 3,215 cc.; sitting down, 3,200 cc.; lying on the back, 2,940 cc.; lying on the right side, 2,935 cc.; lying on the left side, 2,960 cc.; lying on the abdomen, 3,050 cc., and in a half sitting position, 2,995 cc.

Max Pinner.

Vital Capacity in Pulmonary Tuberculosis During Collapse Therapy. H. Sieper, Beitr. z. Klin. d. Tuberk. **65**:725, 1927.

In order to study the influence of pulmonary collapse on the vital capacity in the absence of pulmonary disease, the author had a right-sided pneumothorax induced on himself. It was found that the difference between the vital capacity before and after each inflation was equal to the volume of air introduced into the pleural cavity, as long as the intrathoracic pressure was kept within moderate limits. The vital capacity during collapse increased. This increase is definitely faster than the resorption of the intrapleural air and it reaches the original level before the pneumothorax is completely resorbed. After the resorption of the pneumothorax the vital capacity is greater than before the treatment. The increase in vital capacity is explained by the depression of the diaphragm and by a compensatory increase in the respiratory excursions, which later finds its expression in the circumference of the thorax in inspiration and expiration. In patients with pulmonary tuberculosis the vital capacity following the inflation of air is greater than the difference between the original vital capacity minus the inflated air. This fact is explained in the following way: The pulmonary tissue surrounding tuberculous foci frequently does not participate in the aeration process. The vital capacity of such a patient is therefore smaller than could be expected from the size of his foci. The collapse of such areas does not decrease the vital capacity of the patient. It follows that the vital capacity after the induction of pneumothorax will be higher the more damaged tissue is collapsed in proportion to normal tissue. In the pulmonary patient the vital capacity is increased during treatment by pneumothorax and may reach the same value as before treatment; it may even surpass the latter. After some time the vital capacity remains stable; at this point complete collapse is obtained. Intercurrent pulmonary diseases depress the vital capacity frequently before they can be recognized by physical signs. It is emphasized that careful determinations of the vital capacity are of great prognostic significance during collapse therapy.

Max Pinner.

CARBOHYDRATE METABOLISM IN PULMONARY TUBERCULOSIS. P. HECHT and P. BONEM, Beitr. z. Klin. d. Tuberk. **65**:763, 1927.

Serial examinations of the blood sugar in pulmonary tuberculosis yielded the following results: The dextrose values were never increased over the normal. The normal values in incipient and in inactive cases and in clinically healed patients are high. In extensive and active cases the value usually is close to the lower limit of the normal, and in a certain percentage of cases it is definitely subnormal. After the administration of 20 Gm. of dextrose in hypoglycemic patients, a disturbance in the blood sugar regulation was observed which consisted in a slow increase of dextrose and in a prolonged duration of the hyperglycemic condition, followed by pronounced hypoglycemia. The glycogen content of the liver was determined in normal and in tuberculous guinea-pigs. The average values were 4.215 per cent and 0.739 per cent, respectively. This fact demonstrates that the liver of tuberculous persons has lost the ability to fix glycogen.

MAX PINNER.

ACUTE AND CHRONIC LEUKEMIA FOLLOWING OBESITY CURES. H. CURSCHMANN, Klin. Wchnschr. **6**:245, 1927.

Four patients developed leukemia following severe fasting and prolonged thyroid substance therapy for obesity. The explanation is that a predisposition to leukemia existed and that this was precipitated by the fat cure which upset the balance between the hormonal and blood-forming functions.

J. D. WILLEMS.

Pathologic Anatomy

THE INCIDENCE AND NATURE OF SPLENIC NEOPLASMS. E. B. KRUMBHAAR, Ann. Clin. Med. **5**:833, 1927.

Among 6,500 autopsies at the Philadelphia General Hospital during the past six years, forty splenic neoplasms were encountered, six being primary neoplasms and thirty-four secondary. Two of the primary tumors were benign (angiomas); the other four were sarcomas. Twelve of the thirty-four secondary tumors were some form of sarcoma, twenty-one were carcinomas, and one, a myeloma. Some experimental evidence exists to support the belief that an antagonism exists between neoplasms and splenic tissue. Tumor grafts into the spleen succeed less often and are smaller than in other tissues. After splenectomy, the organism appears more susceptible to tumor growth. Tumor cells are found frequently in the sinuses, but do not produce metastatic growths in the pulp. In several cases of carcinomatosis, nodules in the spleen, grossly diagnosed as metastases, showed few or no neoplastic cells microscopically.

WALTER M. SIMPSON.

LATENT SYPHILIS AS A CAUSE OF HEART DISEASE. R. W. SCOTT, Ann. Clin. Med. **5**:1028, 1927.

At the Cleveland City Hospital during the past seven years there have been over 500 cases of heart disease which came to autopsy. Syphilis appeared to be the chief cause of cardiac death in seventy-five of these cases. Syphilis of the aorta was found in each case. The valve leaflets were involved, or the aortic ring dilated, in all but two cases. Latent syphilis is an important cause of death from heart failure only when it attacks the root of the aorta. Cardiac failure cannot be ascribed to syphilitic changes in the myocardium. Histologic changes in the myocardium are not characteristic, and to regard them as evidence of latent myocardial syphilis seems unwarranted. The earliest and most important sign of syphilitic involvement of the aortic valves, from the standpoint of gross diagnosis, is a widening of the commissures.

WALTER M. SIMPSON.

ELASTIC TISSUE OF THE HEART IN ADVANCING AGE. ADAM MILLER and ORMAN C. PERKINS, Am. J. Anat. **39**:205, 1927.

This article presents the results of studies on the elastic tissue in normal hearts of persons of different ages. The material was prepared by several methods for showing elastic tissue, and the descriptions in the main are written from the specimens which had been stained with Weigert's elastic-tissue stain.

The infant's myocardium contains no elastic tissue; the ventricular endocardium contains only a few fibers, but the atrial endocardium shows a considerable amount of elastic tissue. In middle age (35 years) there is a marked increase of elastic tissue in the atrial endocardium, a slight increase in the ventricular endocardium, and a few elastic fibers appear among the strands of muscle. In old age (85 years) the atrial endocardium is much thicker and shows a decided further increase of elastic material; the ventricular endocardium also contains more elastic fibers, and many fibers are present among the strands of muscle in both atrial and ventricular regions.

The increased elastic tissue in advancing age is interpreted in terms of a compensatory mechanism, the cardiac muscle probably suffering a loss of vital power. Gradation of stainability of the fibrous elements of the connective tissue during the increase of elastic components points to the conclusion that, under rhythmic stress and strain, collagenous fibers are transformed into elastic fibers.

AUTHORS' SUMMARY.

THE INTRACRANIAL TUMORS OF PREADOLESCENCE. HARVEY CUSHING, Am. J. Dis. Child. **33**:551, 1927.

The author presented eighteen cases of intracranial tumors; eleven of these were tumors of the cerebellum, the majority of which took their origin from the roof of the fourth ventricle. Preadolescent tumors are classified in three large groups; gliomas, congenital tumors and tuberculomas, in order of frequency. The gliomas, which constituted 75 per cent of 154 recorded cases in childhood, include malignant and rapidly growing spongioblastomas, which usually occurred in the midcerebellar region, having arisen from the roof of the fourth ventricle, and fibrillary and protoplasmic astrocytomas. The majority of the congenital tumors were supracellar lesions arising from an anlage of Rathke's pouch. Tuberculomas were relatively infrequent and occurred most frequently in the cerebellum.

NEUROCYTOMAS OF THE LEFT SUPRARENAL GLAND WITH METASTASES TO THE LIVER, SKULL AND BONES. CHARLES N. STURTEVANT and THOMAS C. KELLY, Am. J. Dis. Child. **33**:590, 1927.

A case of neurocytoma of the left suprarenal gland is described in which ecchymoses about the eyes and exophthalmia were present before death, and in which there were metastases to the skull, dura, ribs, vertebrae, right innominate vein, right femur and liver.

NONTRAUMATIC DIAPHRAGMATIC HERNIA: REPORT OF A CASE IN A CHILD AGED FOUR YEARS. JEROME S. LEOPOLD, Am. J. Dis. Child. **33**:597, 1927.

A case is described, in which at operation, the greater portion of the stomach, entire small intestine, the ascending and part of the transverse colon, cecum and appendix were found in the left pleural cavity.

PYOPNEUMOTHORAX IN INFANTS. F. ELMER JOHNSON, Am. J. Dis. Child. **33**: 740, 1927.

This report includes a study of ten cases in which pyopneumothorax developed spontaneously during an attack of pneumonia. In the three cases

coming to necropsy the lung showed rupture in the upper lobe, thick pleural exudate with interlobar adhesions, collapse of part of the lung with one or more abscesses and bronchopneumonia. The ages of the infants ranged from 1 month to 3 years.

RUTH E. TAYLOR.

VON JAKSCH'S ANEMIA. THOMAS B. COOLEY, Am. J. Dis. Child. **33**:786, 1927.

The author has come to the conclusion that the disease which should bear the name of von Jaksch's anemia is one of the hemolytic anemias, probably congenital, which appears in infancy or early childhood and is characterized by enlarged spleen and liver, both of which show increase in interstitial connective tissue, and hyperplastic bone marrow.

RUTH E. TAYLOR.

GROWTH OF THE THYMUS: ITS RELATION TO STATUS THYMICOLYMPHATICUS AND THYMIC SYMPTOMS. EDITH BOYD, Am. J. Dis. Child. **33**:867, 1927.

The thymus in the new-born child shows a temporary loss of weight which probably is concomitant with the normal loss in body weight. The fetal type of thymus is broad, the infantile type elongate. This change in form is produced during the first two weeks of life by the expansion of the lungs (Noback). Thymic symptoms may be produced during the first year of life by mechanical pressure of a normal gland on mediastinal structures, especially on the recurrent laryngeal nerve. My records do not show any case in which death was caused by pressure on the trachea by the thymus. The anatomic picture that Paltauf described as that of status thymicolymphaticus represents the normal thymus and lymphoid tissue of the well nourished child. Failure to recognize accidental involution has caused the confusion regarding the weight of the thymus and the misconception, status thymicolymphaticus. The average weight of the thymus found at necropsy in well nourished children is 13 Gm. at birth; 20 Gm. at 6 months, and 35 Gm. at 13 years. The average weight of the thymus found at necropsy in poorly nourished children is 8 Gm. at 2 weeks; 6 Gm. at 6 months, and 13 Gm. at 13 years. In general, the fluctuations in the weight of the thymus at any age are concomitant with fluctuations in body weight. Some illnesses, such as influenza, may affect the thymus before they affect body nutrition. The growth curve of the thymus in a well nourished child is of the same type as that of the lymphoid tissues in general.

AUTHOR'S SUMMARY.

SANGUINEOUS LACRIMATION: REPORT OF A CASE. Z. R. SCOTT, Am. J. Dis. Child. **33**:907, 1927.

A summary of the etiologic factors concerned in the ninteen cases of sanguineous lacrimation found in the literature shows: six cases associated with menstrual disturbances; three cases of emotional strain; one case of rupture of the capillary vessels of the eye; one case of conjunctivitis; one case of tumor of the eyelids; one case probably from the lacrimal gland; one case due to back pressure from the nasal cavity, and five cases, the cause of which are not given. The case reported is one of sanguineous lacrimation resulting from an acute inflammation of the lacrimal gland, associated with an infection of the upper respiratory tract.

AUTHOR'S SUMMARY.

AYERZA'S DISEASE: WITH A REPORT OF TWO CASES. GARNETT CHENEY, Am. J. M. Sc. **174**:34, 1927.

A brief review of the clinical, laboratory and pathologic features of the syndrome known as Ayerza's disease is presented, and it is suggested that this term be restricted to those cases of sclerosis of the pulmonary artery and resulting hypertrophy of the right side of the heart which are due to syphilis.

It has been pointed out that the clinical picture of the black cardiac can develop in a variety of conditions, and there may be sufficient evidence to justify the clinical diagnosis of Ayerza's disease, but one must await a final word from the pathologist. Two case reports are presented. In the first, the diagnosis is definite and the pathologic record complete. The second is not definite, but presents the evidence on which a presumptive clinical diagnosis may be made. A survey of the literature includes all known cases and emphasizes the rarity of the malady. A practically complete bibliography of Ayerza's disease is appended.

AUTHOR'S SUMMARY.

MAINTENANCE OF LEUKOCYTE LEVEL AND CHANGES DURING IRRADIATION: A STUDY OF THE WHITE BLOOD CORPUSCLES APPEARING IN THE SALIVA AND THEIR RELATION TO THOSE IN THE BLOOD. RAPHAEL ISAACS and ARTHUR C. DANIELIAN, Am. J. M. Sc. **174**:70, 1927.

The present work is a quantitative and qualitative study of the leukocytes which appear in the saliva of healthy persons and of those who have certain diseases. The saliva, as it appears at the opening of the ducts, is practically free from leukocytes. The white cells are washed together from the mucous membranes through which they have wandered. The average leukocyte count in the mixed saliva (in health) varies from 5 to 150 (rarely as high as 450) cells per cubic millimeter, the variations appearing during the course of the day, sometimes quite rapidly. The variations in the number of the leukocytes in the saliva accompanies the changes in the number of leukocytes in the blood, but the relation is most commonly a reciprocal one. When a "digestive leukocytosis" fails to show in the blood it is sometimes evident in a great increase in the number of cells in the saliva. All types of white blood corpuscles, and probably blood platelets are found in the saliva, the number varying with the disease. Although the percentage of polymorphonuclear leukocytes bears much the same relation to the other cells in the normal saliva as in the blood, it may be comparatively increased in chronic lymphatic leukemia and similar diseases. When the cells are abundant in the saliva the majority are living, but when they are scanty a greater proportion may not show signs of life. The process of "rigor mortis" of polymorphonuclear leukocytes is described. Some of its stages are suggestive of a reversal of the process of maturation of the myelocytes. The number of leukocytes in the saliva is greatly increased in chronic myelogenous leukemia, often more so when the count is moderate than when it is extremely high. After roentgen-ray treatment there appears to be a great elimination of leukocytes, most of them living, in the saliva. The presence of myelocytes and young polymorphonuclear leukocytes in the saliva suggests that when immature cells enter the blood stream they are eliminated as such, and do not mature in the peripheral circulation. The cells may be greatly increased in number in the saliva in lymphoblastoma. In aleukemic lymphatic leukemia the number of leukocytes per cubic millimeter of the saliva may be greater than that of the blood, the low white blood cell count being associated with the increased rate of elimination. In Hodgkin's disease the elimination of lymphocytes and eosinophils in the saliva may be marked. When leukopenia is accompanied by increased elimination of leukocytes in the saliva, cell production is active, and roentgen-ray irradiation of lesions in the body is not contraindicated. It appears that leukocytosis may occur from increased production of leukocytes or from decreased elimination, and leukopenia from decreased production or from increased elimination. The mucous membranes of the mouth, and probably other parts of the gastro-intestinal tract act as points of elimination of leukocytes, in the general regulatory mechanism which tends to keep the blood elements within certain numerical limits.

AUTHORS' SUMMARY.

REPORT OF A CASE OF CONGENITAL MALFORMATION AND ARRESTED DEVELOPMENT OF THE COLON. G. K. SIMS and H. L. MEYERS, Am. J. Obst. & Gynec. **12**: 887, 1926.

The colon was represented by a cordlike structure, without a mesentery, extending from the ileocecal junction diagonally upward to the crest of the ileum where it widened into a normal bowel. The appendix was attached to the distal end ot the ileum. Microscopic sections did not reveal any lumen in the cord for a distance of 4 cm. from the ileocecal junction.

AN INQUIRY INTO THE CAUSE OF OLIGOHYDRAMNIOS. W. SCHILLER and R. TOLL, Am. J. Obst. & Gynec. **13**:689, 1927.

A patient having oligohydramnios had an associated inflammatory reaction of the placenta, which was most marked on the maternal aspect. The urogenital system of the fetus was malformed. The authors conclude that an endometritis had existed prior to pregnancy, but was not severe enough to prevent implantation of the ovum. The renal anomaly, which consisted in a left aplasia and right hyperplasia, is accounted for on the basis that the decidual inflammation provided inadequate nourishment for the early ovum, affecting the anlage of the metanephrogenic tissue. The inflammation extended from the decidua through the placenta, affecting the chorion, and through the amnion, where the loss of functional epithelium gave rise to the oligohydramnios.

A. J. KOBAK.

ECTOPIC ENDOMETRIUM IN THE OVARY AND INGUINAL CANAL. E. SCHMITZ, Am. J. Obst. & Gynec. **13**:705, 1927.

A chocolate cyst in the right ovary and a tumor mass in the right inguinal region showed ectopic endometrial-like tissue. The mass from the inguinal region was filled with numerous capillary spaces, the endothelium of which had proliferated. These spaces were surrounded by large cells indistinguishable from endometrial stroma cells. Large cell elements were present along the lymphatic spaces. Similar conditions were noted in a portion of the cyst, in which a small vessel showed endothelial proliferation. The author contends that one of two possibilities was taking place, either differentiation of embryonal cells or metaplasia of the endothelial cells of the finer capillaries and lymphatics.

A. J. KOBAK.

INTRATHORACIC ANNULAR SHADOWS. R. S. E. MURRAY, Am. Rev. Tuberc. **15**: 472, 1927.

Precision stereoscopic magnification of shadow detail tends to resolve the intricate pencillings of pulmonary pathologic anatomy into actual structural forms. Annular shadows were found in 47 per cent of the patients examined in whom the condition had been definitely active for a year or more. Eighty per cent of the shadows were definitely due to cavitation.

H. J. CORPER.

ARTIFICIAL PNEUMOTHORAX FOLLOWING SPONTANEOUS PNEUMOTHORAX OF CONTRALATERAL LUNG. HERBERT F. GAMMONS, Am. Rev. Tuberc. **15**:475, 1927.

A case of spontaneous pneumothorax in the good lung is reported which was probably due to traction of pleural adhesions at the base during cough. Deflation and aspiration relieved the symptoms. It was possible to induce pneumothorax on the side opposite to the spontaneous pneumothorax.

H. J. CORPER.

THE FORMATION OF GIANT CELLS IN TISSUE CULTURES AND THEIR SIMILARITY TO THOSE IN TUBERCULOUS LESIONS. WARREN H. LEWIS, Am. Rev. Tuberc. **15**:616, 1927.

Giant cells in tissue cultures were found to resemble closely those in tuberculous lesions. It is apparent that the causes responsible for giant cell formation are not known. Contact with foreign bodies, substances produced by tubercle bacilli and deficient oxygen are possible factors. It is not believed that they are the determining ones, and that the cells that fuse must be in a peculiar state and different from those that do not fuse. The more important factors were not foreign bodies or deficient oxygen, but probably some internal metabolic condition that affected the whole cell, its interior as well as its surface.

H. J. CORPER.

MELANIN PIGMENTATION: A SYSTEMATIC STUDY OF THE PIGMENT OF THE HUMAN SKIN AND UPPER MUCOUS MEMBRANES, WITH SPECIAL CONSIDERATION OF PIGMENTED DENDRITIC CELL. S. WILLIAM BECKER, Arch. Dermat. & Syph. **16**:259, 1927.

By appropriate methods it was demonstrated that the normal (grossly unpigmented) buccal mucosa obtained from fifty-three unselected cases that came to autopsy showed a slight degree of microscopic epidermal pigmentation in 74 per cent of the cases. Pigmentation of the connective tissue was marked in 26 per cent of the cases. Pigmentation of the buccal mucosa, therefore, seems to be a normal condition. This fact explains the increase of pigment in this region in so many pathologic conditions. In the pharynx, which has not been previously studied except with reference to gross macroscopic pigmentation, pigment was found in 21 per cent of the cases. Half of these were in patients who died with generalized malignant growths. The faculty of pigment production appears to be present normally, at least potentially, in the epithelial cells of the pharyngeal mucosa. Pigment was not found in the human esophagus and mammary gland, but was present for a short distance in the superficial lacteal ducts of the nipple. The internal surface of the prepuce in both male and female are normally pigmented. Demonstration of a positive dopa reaction in the pigment cells of both the buccal and the pharyngeal mucosa furnishes added support to Bloch's theory of the fermentative origin of melanin.

Dendritic cells are much more frequent in normal skin than has been generally supposed. They were found in all regions examined. In the cutaneous surface, they vary from 25 per cent of all cases of the nipple and abdomen to 67 per cent of those of the toe; in the mucous surfaces they vary from 21 per cent of all cases of the pharynx to 70 per cent of all cases of the buccal mucosa and 79 per cent of all cases of the inner surface of the prepuce. Dendritic cells vary in size, shape, nature of branching and numerical relation to nondendritic cells in different regions of the skin and mucous membranes, and even in the same location in different persons. Considering only the pigmented sections, they vary from 25 per cent in the nipple and the abdomen to 100 per cent in the pharynx. Dendritic cells, therefore, seem to be a more or less normal (physiologic) factor of ectodermal pigmentation. The morphology of the dendritic cell seems to depend on the nature of the tissue, the thicker the epithelium (buccal mucosa and acanthotic processes, such as condyloma acuminata), the larger and more branched the cells. Less variation occurs in the total dendritic cell pigmentation in the various sections of the same region than in that of nondendritic cells. Evidence suggests that dendritic cells are cells normally present in the basal layer that assume the pigmented dendritic cell form under the influence of some pigment forming impulse (pregnancy in the case of the nipple and generalized malignant growth in the case of the pharynx). Mitotic figures and other evidence of cell division could not be found in the pigmented dendritic cells of the pharynx. The problem of the dendritic cell needs further investigation.

Chromatophores are present in varying degree in all regions studied, and are situated in varying portions of the superficial dermis. The melanin of the deeper cells does not react appreciably to silver salts. The pathologic increase in pigment may be predominantly an increase in pigment in the dendritic cells (acanthotic lesions) or in the nondendritic cells (Addison's disease). A combination of all the methods used in this study, the most valuable of which are the dopa and silver reactions, is necessary for the proper interpretation of normal and pathologic melanin pigmentation.

AUTHOR'S SUMMARY.

CHRONIC SUBDURAL HEMATOMA. C. W. RAND, Arch. Surg. **14**:1136, 1927.

This subject has been reviewed previously by Putnam and Cushing (*Arch. Surg.* **11**:329, 1925), and their article abstracted (ARCH. PATH. **1**:614, 1926). Rand's article is an excellent summary of the clinical picture and the probable pathogenesis. Several cases are presented and analyzed. From these a history of injury has always been obtained and the condition may follow slight or severe trauma. The spinal fluid is first blood-tinged, then xanthochromic and finally becomes clear. Evidence of increased intracranial pressure usually is present. Five of seven patients recovered after operation.

N. ENZER.

Pathologic Chemistry

THE QUANTITATIVE DETERMINATION OF BLOOD AMYLASE WITH THE VISCOSIMETER. ROBERT ELMAN and JOHN M. MCCAUGHAN, Arch. Int. Med. **40**:58, 1927.

A method is described for the quantitative estimation of amylase based on the time required to effect an arbitrary reduction in the outflow time in a viscosimeter of a buffered starch solution. The time values thus obtained were found to vary in simple inverse relation with the concentration of amylase. An arbitrary amylase unit was selected as representing the concentration of enzyme capable of lowering the viscosity of 7 per cent starch solution by 20 per cent in one hour. Using this standard, we found that the amylase content of the plasma of normal dogs fell between 1.5 and 2.5 units. Fasting did not alter this range, and meals did not have any influence. In three instances in which the total pancreatic juice was draining to the outside, the amylase content of the plasma was within these same limits. The method has proved simple and easy to carry out, and would seem to be readily adopted for routine use.

AUTHORS' SUMMARY.

ON THE ISOELECTRIC PRECIPITATION OF PEPSIN. F. FENGER and R. H. ANDREW, J. Biol. Chem. **73**:371, 1927.

The pepsin-producing glandular tissues from the stomach of hogs are removed within a few minutes after the animals are slaughtered and transferred to the chill room, trimmed free from fat and muscle, washed and brushed with ice water until all adherent mucin is removed and finely minced. Four hundred cubic centimeters of 2 per cent hydrochloric acid is poured into each kilogram of hash, with stirring, and the mixture is allowed to stand over night. Fifty per cent of acetone is then added and the resulting precipitate removed by filtration. The p_H of the clear filtrate should lie between 3.4 and 3.6. The pepsin fraction separates as a nearly white, adhesive sediment when the acetone concentration is increased to 75 per cent. The precipitated pepsin is dissolved in acidulated water to a final p_H of from 1.8 to 2, filtered, and dialyzed against running water at from 5 to 10 C. The first fraction, separating at a p_H of from 2.4 to 2.5, is the most nearly pure. Other fractions precipitate at a p_H of from 2.5 to 3 and from 3 to 3.85. They are collected by centrifugalization, washed with distilled water, and desiccated in vacuo at room temperature. The purified enzyme is a nearly ash-free protein, insoluble in distilled water. Its iso-electric range is from p_H 2.4 to 3.85, and the pro-

teolytic activity of the fractions obtained varies from 1:70,000 to 1:45,000 (U.S.P. assay). The purified material is unstable and does not submit itself to further purification by reprecipitation methods.

ARTHUR LOCKE.

FACTORS INVOLVED IN THE REACTION CHANGES OF HUMAN SALIVA. G. W. CLARK and K. L. CARTER, J. Biol. Chem. **73**:391, 1927.

The physicochemical processes involved in the formation and deposition of calculus on the teeth are not yet understood. It has been suggested by some investigators that the deposition may be associated with an increase in the p_H of the saliva such as would cause the precipitation of calcium mucinate and tricalcium phosphate. These substances separate from saliva when the p_H reaches 8 or more, but do not redissolve on subsequent acidification to p_H 7 or less. Saliva contains from one-third to one-fifth as much carbon dioxide and from three to six times as much inorganic phosphate as does blood plasma. Its p_H varies from an average value of 6.6. Samples of saliva may stand for several hours without showing appreciable changes in carbon dioxide content, possibly due to an equilibrium between the rate of its escape and the rate of its formation by enzymic processes. The ammonia content is slightly increased as the result of a combined bacterial and enzymic action. Saliva is a well buffered mixture and can neutralize large quantities of hydrogen and hydroxyl ions without appreciable changes in p_H. The conclusion is drawn that the p_H changes requisite for the deposition of calculus must involve other constituents than carbon dioxide and ammonia. [The possibility that the p_H of the interfacial film at the liquid surface between the saliva and the teeth may be different from that of a volume of saliva in vitro has apparently not been considered. The interfacial p_H in solutions of egg albumin and blood serum is so much less than the p_H existing throughout the solution as to cause the denaturation and precipitation of a solid film of protein at the liquid surface [Cf. Ramsden, *Ztschr. f. phys. Chem.* **47**:336, 1904].

ARTHUR LOCKE.

ALCOHOLIC CONTENT OF NORMAL PLACENTAL TISSUE. W. D. MCNALLY, H. C. EMBREE and C. A. RUST, J. Biol. Chem. **74**:219, 1927.

The normal alcoholic content of human placental tissue varies from 0.0008 to 0.0052 per cent.

ARTHUR LOCKE.

THE EFFECT OF INSULIN INJECTED INTO THE CEREBROSPINAL FLUID. J. V. SUPNIEWSKI, Y. ISHIKAWA and E. M. K. GEILING, J. Biol. Chem. **74**:241, 1927.

The injection of insulin into the cerebellar cisterna has little if any hypoglycemic effect. This may indicate that the insulin molecule is of a much larger dimension than that of epinephrine hydrochloride or pituitary, which later diffuse readily from the cerebrospinal fluid into the blood stream.

ARTHUR LOCKE.

THE DETERMINATION OF CALCIUM IN WHOLE OXALATED BLOOD. C. S. ROTHWELL, J. Biol. Chem. **74**:257, 1927.

The calcium of whole, oxalated blood may be readily determined if the blood is first treated with trichloracetic acid for the solution of calcium oxalate and the precipitation of the blood proteins.

ARTHUR LOCKE.

THE QUANTITATIVE DETERMINATION OF IRON IN TISSUES. R. P. KENNEDY, J. Biol. Chem. **74**:385, 1927.

A method is described for the quantitative estimation of iron in tissue. The tissue is digested in a mixture of perchloric and sulphuric acids, the

digest diluted to a measured volume, and an aliquot portion treated with a concentrated solution of sodium sulphocyanate. The resulting ferric salt is extracted with amyl alcohol, and the color of the alcoholic solution compared with that of a similar solution containing a known amount of iron. Iron as sulphocyanate has about 10 per cent more color than when combined as hemoglobin. The values obtained for blood agree closely with values obtained by the estimation of hemoglobin and oxygen capacity. The iron content of several preparations of kidney, spleen, liver, brain, heart and skeletal muscle is reported.

ARTHUR LOCKE.

THE ANTISTERILITY VITAMINE FAT SOLUBLE E. HERBERT MCLEAN EVANS and GEORGE O. BURR, Mem. Univ. Calif. **8**:145, 1927.

A brief description of the steps in the purification of vitamin E has been given. The results have been secured many times, and there can be no doubt that there is a substance present in the active fractions which is specific for curing a specific type of sterility induced by certain purified diets. The cure has repeatedly been effected by as little as 5 mg. of the concentrated fractions fed on the day of positive mating. Controls have never given litters. The best fractions are still too conglomerate for trustworthy speculation concerning the true nature of the vitamin. At one time we attempted to follow the active material by chemical tests, but this proved uncertain. A study of stability, solubility and properties in fractionation shows it to be a fat soluble material, possessing a stability exceptional for a compound so active biologically. The solubility is rather remarkable in that it is completely soluble, even in 76 per cent alcohol and at the same time soluble in pentane, chloroform, dry ether, and other anhydrous solvents. The stability and behavior points to a material similar to vitamine A, which Drummond has greatly concentrated; yet the two are readily proved distinct biologically. Cod liver oil has been fed in high doses without effecting a cure of sterility, and its nonsaponifiable matter is well known to be extraordinarily rich in A. On the other hand, our fractions from wheat germ oil do not prevent or cure the pathologic condition due to A deficiency. Recently Doisy, Allen, Ralls, and Johnston have aroused interest in the ovarian hormone, which had been previously studied by Herrmann. They have confirmed Herrmann's observation that the hormone is not cholesterol or its esters, and they believe that it may be nonsaponifiable. But Dickens, Dodds, and Wright do not find the hormone stable to saponification. Whether it is stable to ordinary saponification or not, the great stability to temperature and the volatility are properties which remind us of vitamines A and E. Herrmann distilled his active fraction at 193 C. (0.06 mm. pressure) without previous saponification. It is rather remarkable that the ovarian follicular hormone, vitamin A, and vitamin E all present this similarity. Each has a special relationship to reproduction. We are unable to make further statements concerning the chemical groups concerned in the makeup of vitamin E until results from experiments now in progress are available. Yet the foregoing preliminary steps in its isolation have been so repeatedly confirmed that we feel that we may regard them as established.

AUTHORS' SUMMARY.

CHEMICAL STUDY OF THE MANOILOV TEST FOR THE DIFFERENTIATION OF THE SEXES. K. G. FALK and J. LORBERBLATT, Brit. J. Exper. Biol. **4**:305, 1927.

The chemistry of the Manoilov test is discussed, and simplication of the procedure is recommended. Cases of reverse reaction are noted.

GLYCEMIA IN CHRONIC TUBERCULOSIS. M. BOROCK, P. WOWSI and G. RANZMANN, Beitr. z. Klin. d. Tuberk. **65**:769, 1927.

In regard to the dextrose values in the blood, patients with pulmonary tuberculosis can be divided into two groups, one with decreased values and the other with normal or slightly increased values. The limit between the two

groups is represented by a sugar content of from 70 to 80 mg. per hundred cubic centimeters. The second group as a whole is prognostically more favorable.

MAX PINNER.

PLASMA PROTEINS IN SCARLET FEVER. B. STEINER, Jahrb. f. Kinderh. **115**:348, 1927.

At the onset, the plasma contained a large amount of fibrinogen, which decreased gradually in uncomplicated cases. In complicated cases the amount increased.

THE IMPORTANCE OF THE HYDROGEN ION CONCENTRATION IN THE WASSERMANN REACTION. C. STERN, Klin. Wchnschr. **6**:310, 1927.

The p_H of blood serums in which the Wassermann reaction was positive ranges from 7.2 to 7.8.

J. D. WILLEMS.

THE INFLUENCE OF ELECTROLYTES ON THE HUMAN BLOOD SUGAR. HASENÖHRL and F. HÖGLER, Klin. Wchnschr. **6**:399, 1927.

Sodium, potassium and calcium salts were given to normal and to diabetic patients together with and without atropine, epinephrine and insulin. There was no specific action on the blood sugar level attributable to the electrolytes.

J. D. WILLEMS.

THE CALCIUM AND POTASSIUM CONTENT OF THE BLOOD. ESKIL KYLIN, Acta med. Scandinav., Suppl. **19**:1, 1927.

The normal content of calcium in the blood is between 10.6 and 12 mg. per hundred cubic centimeters, the average being 11.13. In childhood the amount is larger than later. The normal potassium content varies between 18 and 24 mg. per hundred cubic centimeters of blood; the average is 20.7. The normal relation between potassium and calcium is approximately as 2 to 1. In certain diseases this relation may be disturbed in bronchial asthma, essential hypertension potassium is increased and calcium is diminished, but in diabetes, calcium is increased. In persons with a high potassium ÷ calcium quotient the reaction to epinephrine is vagotonic, while in persons with a low quotient, it is sympathecotonic.

Microbiology and Parasitology

BACTEREMIA IN DIPHTHERIA: INVASION OF THE BLOOD STREAM BY THE KLEBS-LOEFFLER BACILLUS AND ASSOCIATED ORGANISMS. EDGAR MARTMER, Am. J. Dis. Child. **33**:895, 1927.

Cultures were made in a series of forty cases, and six of these showed an infection in the blood stream. Three presented pure cultures of *Bacillus diphtheriae* and the others a hemolytic streptococcus. These cultures were all positive at the end of the first twenty-four hour period of incubation. It is interesting to note that two of the cases presenting infection with *Bacillus diphtheriae* were true hemorrhagic diphtheria, and the third case showed hemorrhages from the nose and oral mucous membranes before death. None of the patients who showed infection with the streptococcus had hemorrhages, and they were all of the so-called septic type of diphtheria.

THE EFFECTS OF CHANGES IN THE SUGAR CONTENT OF THE BLOOD ON BIRD MALARIA. MARY STUART MACDOUGALL, Am. J. Hyg. **7**:635, 1927.

A complete record of experiments in modifying the course of infections in bird malaria by changing the sugar content of the blood is presented. The

conclusions reached in the preliminary work seem to be justified by more extensive experiments, namely, that the increase in the sugar content of the blood brings about a condition favorable for the parasite in bird malaria, and that a decrease in the blood sugar by the use of insulin creates a condition unfavorable for the parasite.

COCCIDIOIDAL GRANULOMA. DAVID RIESMAN and FLORENCE E. AHLFELDT, Am. J. M. Sc. **174**:151, 1927.

A case of coccidioidal granuloma is reported from Pennsylvania, and eighty-seven cases from the literature are reviewed briefly.

BACTEREMIA DUE TO BACILLUS FECALIS ALKALIGENES. W. S. WYATT, Am. J. M. Sc. **174**:181, 1927.

The symptoms of bacteremia resemble those of typhoid fever. The prognosis is favorable (one death in forty cases). The diagnosis may be made by blood cultures and agglutination.

REACTION OF GUINEA-PIGS TO GRADED CONJUNCTIVAL INFECTIONS WITH TUBERCLE BACILLI. S. LYLE CUMMINS, Am. Rev. Tuberc. **15**:306, 1927.

Preinfection with living tubercle bacilli introduced through a "natural" portal of entry, the conjunctival mucous membrane, leads, under certain circumstances, to an enhanced resistance to subsequent infection with a lethal dose. Preinfecting doses of low infective potential appear insufficient to lead to a satisfactory degree of resistance, while high infective doses tend to induce lesions so extensive as to be liable to activation by subsequent reinfection. Between these there is a zone of optimum dosage leading to increased resistance, as indicated by marked prolongation of the survival period after the lethal dose. An attenuated strain appears more effective in producing increased resistance than a virulent strain. In tuberculosis induced by conjunctival instillation, the priority of lesions at the portal of entry and in the neighboring lymph nodes, respectively, depends chiefly on the infective potential of the bacillary emulsion employed; lesions of the eye preceding or simultaneous with lesions of the lymph node occur when the infecting dose is large, while lesions of the lymph node show priority to lesions of the eye when the dose is moderately small. When conjunctival infection is induced by the installation of successive small doses repeated at weekly intervals, the guinea-pigs fall into a state of general ill health and tend to die early, recognizable tuberculous lesions being rare or absent. In a small group of animals infected by this method, the production of resistance to a subsequent lethal infection was not appreciable, either in enhanced survival capacity or in a more chronic type of disease.

H. J. CORPER.

SOME RELATIONS OF VITIATED AIR AND OF INADEQUATE FEEDING TO EXPERIMENTAL TUBERCULOSIS. HENRY SEWALL, Am. Rev. Tuberc. **15**:328, 1927.

In normal guinea-pigs the acquirement of tuberculosis by contagion depends on two factors, the duration and the intensity of the exposure. Guinea-pigs exposed to highly vitiated air early in the course of induced tuberculosis show a preponderant deposition of tubercle in the lungs as contrasted with other organs. Repeated drastic exposures of normal guinea-pigs to vitiated air did not increase their liability to contract tuberculosis by contagion from infected animals. Guinea-pigs maintained on a diet containing a minimum of green food, deficient in vitamin, did not manifest greater susceptibility to the acquirement of tuberculosis by association with tuberculous animals than well fed guinea-pigs under similar conditions.

H. J. CORPER.

BRONCHOPULMONARY SPIROCHETOSIS. DAVID T. SMITH, Am. Rev. Tuberc. **15**:352, 1927.

In 150 cases of uncomplicated pulmonary tuberculosis, 6 cases of bronchial asthma and 5 cases of mycotic infection of the lung, spirochetes and fusiform bacilli were absent from the sputum on repeated examination. There is a group of apparently unrelated pulmonary conditions in which spirochetes, fusiform bacilli and cocci are constantly present in the sputum. These micro-organisms are identical to those commonly present in the mouth, and this is the probable source of the pulmonary infection. This view receives support from the production of pulmonary abscess and pulmonary gangrene produced in mice, guinea-pigs and rabbits by intratracheal inoculations of material recovered from the gums of patients suffering from severe pyorrhea. There is reason to assume that bronchial spirochetosis may be the cause of primary bronchiectasis. In 12 cases of bronchiectasis spirochetes, fusiform bacilli and cocci were recovered from the sputum. An analogy is drawn between the bronchus and the artery with consequent aneurysms following infection with *Treponema pallida*. The marked improvement that occurs in some cases of bronchiectasis following treatment with neoarsphenamine lends support to this analogy.

H. J. CORPER.

AN ETIOLOGICAL AGENT IN BRONCHOMYCOSIS. G. I. WALLACE and F. W. TANNER, Am. Rev. Tuberc. **15**:373, 1927.

Certain yeast-like fungi cause a pulmonary infection simulating clinical tuberculosis. A case is reported in which an organism, probably *Monilia albicans*, was isolated, and potassium iodide greatly improved the patient. The organism reported differs in some respects from *Monilia albicans* but not enough to establish a new species.

H. J. CORPER.

THE BIOLOGY OF THE TUBERCLE BACILLUS. I. HYDROGEN-ION CONCENTRATION PRODUCED BY SOME MEMBERS OF THE GENUS MYCO-BACTERIUM. JOHN WEINZIRL and FLORENCE KNAPTON, Am. Rev. Tuberc. **15**:380, 1927.

Fifteen species and strains of acid-fast bacteria of the genus *Mycobacterium* were grown on a synthetic medium containing either dextrose, mannite, lactose or glycerine, and the p_H curve was determined. On dextrose, mannite and lactose all the micro-organisms failed to produce acid, but the alkalinity increased markedly. On glycerine all the micro-organisms produce acidity, and a direct correlation of acid production with growth activity was found regardless of species or strain. The glycerine-fermenters were of two types: in one the acidity became permanent, and in the other the acidity receded, the culture finally becoming markedly alkaline. The micro-organisms which produced permanent acidity were virulent, while those producing a recession of the acidity to alkalinity were avirulent regardless of species or strains.

H. J. CORPER.

THE VARIABILITY OF THE LOCALIZATION OF TUBERCULOSIS IN THE ORGANS OF DIFFERENT ANIMALS. V. THE SIGNIFICANCE OF LOCALIZATION AND DEVELOPMENT OF THE BACILLI, AND OF THE CELLULAR REACTION IN MAN AND ANIMALS. H. J. CORPER, MAX B. LURIE and NAO UYEI, Am. Rev. Tuberc. **15**:389, 1927.

Among the factors controlling organic susceptibility to tuberculosis in man and animals there are preeminently: (1) the distribution of the bacilli to the various organs; (2) the growth of the tubercle bacilli in the organs of the body, as controlled by the oxygen tension of its source of oxygen, and (3) the ability of the cells of origin of the tubercle in the various organs of the different species to destroy the tubercle bacilli, as is indicated by the organic cellular reaction.

H. J. CORPER.

DIPHTHERIA INFECTION OF THE MIDDLE EAR AND MASTOID. JAMES B. COSTEN, Arch. Otolaryng. **5**:119, 1927.

Two cases of diphtheritic infection of the middle ear and mastoid are reported. In each the infection was of long duration before its nature was recognized, and in each the structure of the mastoid was destroyed and replaced by a pyogenic membrane. This destruction was much worse than the symptoms seemed to indicate. If pus from more infections of the mastoid and middle ear were cultivated on special mediums, it is possible that more cases of diphtheritic infection of these structures would be recognized.

A PATHOGENIC LUMINESCENT BACTERIUM. O. L. INMAN, Biol. Bull. **53**:197, 1927.

Amphipod *Crustacea* are the host of *Bacterium giardi* which becomes luminous under certain conditions and may kill the sand flea. This bacterium, if isolated in pure culture and grown on peptone pea water agar of p_H 8.1 becomes luminous within twenty-four hours and may be kept so by frequent transfer for at least two years.

AUTHOR'S SUMMARY.

A STUDY OF FOWL PARALYSIS (NEUROLYMPHOMATOSIS GALLINARUM). ALVIN M. PAPPENHEIMER, LESLIE C. DUNN and VERNON CONE, Bull. 143, Storrs Agricultural Experiment Station, Storrs, Connecticut, 1926.

Fowl paralysis (neurolymphomatosis gallinarum) is a disease entity, with characteristic clinical and pathologic features. The disease occurs in all parts of the United States, Holland, Austria and probably South America. The disease appears to be endemic in certain foci. Having once appeared, the disease tends to persist through successive years. It occurs with about equal frequency in both sexes; all common breeds may be affected. Symptoms appear between the third and eighteenth month. Typical clinical cases have not been observed outside of these limits. The conspicuous symptoms are (*a*) asymmetrical partial and progressive paralysis of wings and both legs, and rarely of the muscles of the neck and (*b*) occasional gray discoloration of the iris, with blindness. Nutrition is usually preserved. The duration is variable; the outcome is usually fatal, but spontaneous recovery may rarely occur.

The principal pathologic changes are found in the nervous system. In the peripheral nerves, the essential feature is an intense infiltration of lymphoid, plasma cells and large mononuclears. This is accompanied by a myelin degeneration in the more advanced lesions, but the cellular infiltrations appear to precede the degenerative changes. In brain and cord and meninges, there are similar infiltrations predominantly perivascular. Infiltrations of the iris with lymphoid and plasma cells are found in the cases showing gross discoloration of the iris. Visceral lymphomas, originating in the ovary, are associated in a certain percentage of the cases. Evidence is presented in favor of the view that this association is not accidental, and that the lymphomas are a manifestation of the disease. Infiltrations of the spinal cord and brain, rarely of the peripheral nerves, are frequently present in birds showing no clinical symptoms. These are interpreted as mild cases of the same disease.

No micro-organisms have been demonstrated in the tissues or by cultural methods. The disease is transmissible to other chickens by subdural or intramuscular injection of suspensions of the nervous tissue of paralyzed birds. Only a certain proportion, not over 25 per cent, of chickens develop the disease after inoculation. This is taken to indicate a widespread immunity, either natural or acquired in the course of the experiment. No relation has been found between paralysis and infestation with coccidia or intestinal worms.

The name neurolymphomatosis gallinarum is suggested for this disease.

AUTHORS' SUMMARY.

SPIROCHETAL JAUNDICE. HARRY H. TOWLER and JOHN E. WALKER, J. A. M. A. **89**:86, 1927.

A case is described from which *Leptospira icterohaemorrhagiae* was cultivated on guinea-pig inoculation. This is apparently the sixth proved case of spirochetal jaundice to be reported in North America. Typical cases of spirochetal jaundice show a fairly definite clinical syndrome, consisting of sudden onset, fever and chills, prostration and severe muscle pains, jaundice appearing the fifth or sixth day. Because of the occurrence of atypical cases, laboratory control of the diagnosis by guinea-pig inoculations (early) or examination of urinary sediment (late) is necessary.

Spirochetal jaundice is probably prevalent in the United States, though it includes only a small proportion of cases classified as infectious jaundice (of unknown etiology) before the discovery of *Leptospira icterohaemorrhagiae*.

A review of the literature indicates that the disease is usually associated with polluted water or soil, possibly being caused by leptospiras living free in nature. It is also possible that the rôle played by rats in the dissemination of the disease has been overemphasized.

AUTHORS' SUMMARY.

LEPTOSPIROSIS ICTEROHAEMORRHAGICA. E. H. CUSHING, J. A. M. A. **89**:1041, 1927.

Two sporadic cases of leptospirosis icterohemorrhagica have been studied recently. Cultures from the urine yielded the organisms in both cases and from the cerebrospinal fluid in one case.

AUTHOR'S SUMMARY.

ACTINOMYCOSIS. J. T. CHRISTISON and MARGARET WARWICK, J. A. M. A. **89**:1043, 1927.

A case is described of diffuse actinomycosis of the lungs and of both suprarenals in a boy, 8 years of age.

EXPERIMENTAL SORE THROAT. GEORGE F. DICK and GLADYS HENRY DICK, J. A. M. A. **89**:1135, 1927.

Just as it was shown by experiments reported in 1921 and 1923 that the scarlet fever streptococcus may cause sore throat without exanthem, it is now demonstrated that the hemolytic streptococcus found in erysipelas may cause acute anginas resembling ordinary sore throat or tonsillitis without the skin manifestations of erysipelas.

AUTHOR'S SUMMARY.

ETIOLOGY OF MEASLES. W. E. GRAY and LOIS A. DAY, J. A. M. A. **89**:1206, 1927.

Of the throat cultures from early cases of measles, 98 per cent showed a green-producing aerobic gram-positive diplococcus usually as the predominating organism. There is reason to believe that there are forms small enough to be filter passers. The type of colony found in the throat changes during convalescence. Smears from the throat of patients with early measles show the diplococci predominating. The filtrate from throat washings causes a febrile response and a definite rash when injected into rabbits intratracheally or intravenously. Some rabbits are apparently not susceptible to measles. About 50 per cent of patients with measles show green diplococci in the conjunctival secretions during the first forty-eight hours of the rash. Blood cultures were positive in five of fifteen cases studied, showing a green diplococcus similar to that found in the throat and conjunctival secretions. The organisms were facultative anaerobes. Seven strains have produced febrile responses and cutaneous rashes in rabbits when injected intravenously, the febrile response falling between the seventh and thirteenth days after inoculation. The organism was recovered from the heart blood in one animal. Passage through four successive rabbits has been made. Salicin appears to be of value in differentiating the diplococci of measles from *Streptococcus viridans*.

AUTHORS' SUMMARY.

STUDIES ON PATHOLOGIC B. COLI FROM BOVINE SOURCES. THEOBALD SMITH and RALPH B. LITTLE, J. Exper. Med. **46**:123, 1927.

Broth filtrates, 24 and 48 hours old, of strains of *Bacillus coli* from the ileum of scouring calves were highly toxic for young calves, older calves and cows also when injected intravenously. Subcutaneously, the filtrate was without visible effect.

THE SURFACE COMPOSITION OF THE TUBERCLE BACILLUS AND OTHER ACID-FAST BACTERIA. STUART MUDD and EMILY B. H. MUDD, J. Exper. Med. **46**:167, 1927.

Acid-fast bacteria in the boundary surface between salt solution and a test oil(tricaprylin) are spontaneously wet and enveloped by the oil. This behavior contrasts with that of all other cells studied by the method of interfacial tension. Four strains of human tubercle bacillus and an atypical bovine strain are an exception to the first statement. These have possessed stability in the saline-oil interface; this stability is slight, however, and not comparable with that of nonacid-fast bacteria. Acid-fast bacteria subjected to prolonged extraction with alcohol show resistance to wetting by oil comparable to that of nonacid-fast bacteria. These "defatted" bacteria, nevertheless, retain their acid-fast staining properties. Acid fastness cannot then depend on the integrity of a surface membrane. Study of the cataphoresis of acid-fast bacteria by Freund has rendered the presence of protein in the surface highly probable. We are forced then to regard the surface of acid-fast bacteria as complex, containing at least lipoid and protein. Not improbably carbohydrate is also present.

AUTHORS' SUMMARY.

FOOD-POISONING DUE TO BACILLI OF THE TYPE B. MORBIFICANS BOVIS (BASENAU). A. F. SLADDEN and W. M. SCOTT, J. Hyg. **26**:111, 1927.

An outbreak of food-poisoning is described in which the *Bacillus morbificans bovis* (Basenau) was the causal agent. The position of this type in the *Salmonella* group as classified by Bruce White has been confirmed by analysis of the antigenic properties and agglutination reactions (including absorption of agglutinin) of the strains isolated in the outbreak.

AUTHORS' SUMMARY.

THE BACTERIOPHAGE: A METHOD OF ISOLATION. ALBERT F. DE GROAT, J. Immunol. **14**:175, 1927.

The lysis which occurs in the d'Herelle-Twort phenomenon is preceded by an intimate fixation of the lytic agent to the organism, and only if the organism is living. There is no increase in the bacteriophage except as a result of bacterial growth. The bacteriophage may be freed from *Bacillus coli* in salt solution followed by filtration so that it can be obtained in nearly a pure solution.

A NEW AGAR-DYE DIFFERENTIAL MEDIUM FOR THE COLON-TYPHOID GROUP WITH SPECIAL REFERENCE TO ITS USE IN WATER ANALYSIS. A. J. SALLE, J. Infect. Dis. **41**:1, 1927.

A new agar-dye differential medium for the identification of the members of the colon-aerogenes-typhoid group is described. The medium contains peptone (Difco), 5 Gm.; K_2HPO_4, 5 Gm.; KH_2PO_4, 1 Gm.; distilled water 1,000 cc.; agar, 20 Gm.; lactose, 5 Gm.; erythrosin (2 per cent aqueous), 20 cc.; methylene blue (1 per cent aqueous), 10 cc.; bromcresol purple (1 per cent aqueous), 20 cc., and by its use two tests are incorporated in one operation, thereby shortening the period of a complete water analysis by twenty-four hours. Dextrose broth cultures may be dispensed with. *Bacillus coli* and *Bacillus aerogenes* are sharply differentiated on this medium because of distinct differences in their carbohydrate metabolism.

AUTHOR'S SUMMARY.

THE RELATIONSHIP BETWEEN THE INTRACELLULAR GLOBULIN AND THE TOXIN OF CHLORINE BOTULINUM. CASPER I. NELSON, J. Infect. Dis. **41**:9, 1927.

This study does not answer the questions suggested by the consideration of the problem with finality, but the results appear to warrant the conclusions that the toxin of chlorine botulinum is elaborated within the cell in intimate association with the characteristic bacterial globulin; its appearance in the surrounding medium is associated with the globulin with which it is still bound, and is accompanied by cell mortality or disintegration, so that in this sense the toxin is not in itself a true secretion; and the toxin is evidently not identical with the intracellular globulin since it can be freed from the associated globulin by peptic digestion.

AUTHOR'S SUMMARY.

AN ACID-FAST ORGANISM ISOLATED FROM A MOUSE. MYCOBACTERIUM MURIS N.SP. JAMES S. SIMMONS, J. Infect. Dis. **41**:13, 1927.

No tubercle bacilli were found in smears from the organs or gastro-intestinal contents, or in cultures from the gastro-intestinal contents of 100 wild, gray mice caught in a hospital for tuberculous patients. A related saprophytic, acid-fast organism which was isolated from the intestinal contents of one mouse and observed for more than two years, was similar to *Mycobacterium* tuberculosis in morphology, staining reactions, slowness of growth, and requirements in mediums for growth. Transfers which have been carried on for two years, however, produced a yellowish tan pigment on glycerol agar. The organism was not pathogenic for white mice, guinea-pigs or rabbits and produced only a local lesion in a chicken.

In consideration of the characteristics and of the source of this organism (from Mus musculus) the name *Mycobacterium muris* is proposed.

AUTHOR'S SUMMARY.

SYNTHETIC MEDIUMS IN THE IDENTIFICATION OF THE TYPHOID-PARATYPHOID BACTERIA. LUTHER THOMPSON, J. Infect. Dis. **41**:16, 1927.

Forty-nine cultures of typhoid and paratyphoid bacteria were tested for their ability to grow in synthetic mediums to which various substances were added as the source of nitrogen. Valine and glutamic acid hydrochloride were selected as the most suitable among the compounds tried for differentiation of members of this group. With valine, growth was obtained in 3 per cent of the typhoid cultures, in 10 per cent of the paratyphoid A cultures, and in 100 per cent of the paratyphoid B cultures. With glutamic acid hydrochloride, the percentages of positive growth were: typhoid 18 per cent; paratyphoid A 80 per cent, and paratyphoid B 100 per cent. Sixteen cultures of nonlactose-fermenting gram-negative bacilli, other than the typhoid and paratyphoid cultures, were tried on these two mediums for comparison. The reactions seemed specific for each species tried. Synthetic mediums could be used to advantage as an additional cultural test in the identification of the bacteria studied.

AUTHOR'S SUMMARY.

THE PAUL TEST IN THE DIAGNOSIS OF SMALLPOX. JOHN A. TOOMEY and JOHN A. GAMMEL, J. Infect. Dis. **41**:29, 1927.

A series of eighty cases of smallpox is reported, of which forty-five gave positive Paul tests. Paul's test when present, may be considered pathognomonic of smallpox.

AUTHORS' SUMMARY.

TUBERCULOSIS IN GUINEA-PIGS AFTER TREATMENT WITH TUBERCLE BACILLI MADE NONACID-FAST WITH OLEIC ACID. F. A. MCJUNKIN, J. Infect. Dis. **41**:45, 1927.

Cultures of tubercle bacilli may be made nonacid-fast by incubating them with 2 per cent oleic acid in 80 per cent ethyl alcohol, and by neutralization of

the oleic acid with sodium hydrate and by dilution with distilled water moderately heavy suspensions of the nonacid-fast bacilli may be obtained in a concentration of about 0.25 per cent of sodium oleate.

The suspension of nonacid-fast tubercle bacilli may be injected into large guinea-pigs without causing loss of weight and with no adverse effect on their general health. Guinea-pigs so treated become infected when subsequently inoculated with living bacilli, but the infection appears to progress less rapidly with the formation of fewer and smaller tubercles in the organs and with greater transformation of epitheloid cells into reticular tissue, than in untreated guinea-pigs. From the data now at hand it seems probable that the favorable effect of the treatment is seen best in large guinea-pigs about four weeks after inoculation.

AUTHOR'S SUMMARY.

A PHARMACOBACTERIOLOGIC STUDY OF AFRICAN POISONED ARROWS. IVAN C. HALL and RICHARD W. WHITEHEAD, J. Infect. Dis. **41**:51, 1927.

Attention is again called to the general recognition that wounds by arrows, poisoned or otherwise, are likely to be infected wounds. It is surprising that so few bacteriologic studies of such wounds have been made, comparable with those on bullet and shrapnel wounds and that bacteriologic studies of poison arrows are not recorded anywhere in the available literature.

The present study deals with six African bushman arrows obtained by Dr. C. E. Cadle during the Denver African Expedition of 1925 from Kalahari, Ovachimba and Heikum tribes. The probably complex nature of the poison is suggested. Only the Heikum arrows had poison on them. There was no evidence of alkaloidal poisons. The poison was separated into amorphous and crystalline fractions, the former about one-half as toxic as the latter. The crystalline fraction was fatally toxic for frogs in doses of from 0.00039 to 0.00044 mg. per gram weight of the frog. Both fractions behaved alike, killing guinea-pigs, cats and frogs by stopping the heart in marked ventricular systole. The poisons could not be identified with any known drugs but resembled the glucoside ouabain in some respects. Two kinds of crystals were noted, but the small amount available precluded separation.

All of the arrows, except the smaller Heikum arrow had pathogenic bacilli on their points in addition to the nonpathogenic "hay bacilli"; the obligate anaerobes (*Bacillus centrosporogenes, B. bifermentans, B. sporogenes, B. nonfermentans,* n. sp., *B. subterminalis,* n. sp.) and the aerobes (*Staphylococcus albus, Streptococcus fecalis,* and *Streptococcus mitis*) occurred as indicated. The pathogens were *B. histolyticus, B. novyi, B. septicus* and *B. welchii.* All of the infected arrows had *B. histolyticus* on them, and the special difficulties encountered in the isolation of this organism in pure culture from mixtures led to the development of a special technic for this purpose, utilizing the fact that *B. histolyticus* is a facultative aerobe, rather than an obligate anaerobe as generally supposed.

AUTHORS' SUMMARY.

A STUDY OF LEPTOSPIRA ICTEROHAEMORRHAGIAE. VIRGINIA LANGWORTHY and ANNA C. MOORE, J. Infect. Dis. **41**:70, 1927.

From a review of the literature it is evident that leptospiral infection, which is designated by the Japanese as spirochetosis icterohemorrhagica, is distinct from other forms of so-called infectious or epidemic jaundice. Despite the variations which occur in individual instances, the clinical manifestations in groups of cases mark spirochetosis as an acute infection with severe toxic effect on the entire organism, characteristically indicated by complete and sudden prostration, a marked febrile reaction, intense muscular pains, hemorrhage, jaundice and nephritis. Epidemiologically, also, spirochetosis is unique; it occurs sporadically, or in localized groups of cases, almost exclusively in persons living in an unsanitary environment in which wild rats, which are carriers of the infectious agent, are apt to be numerous.

The investigation of the jaundice outbreak in New York State failed to reveal the presence of *L. icterohemorrhagiae* in the blood or urine of persons affected, or any immunologic reactions to this organism with the serums of those recovering from the disease. Moreover, the clinical and epidemiologic features of this outbreak differed essentially from those of spirochetosis. Its etiology, therefore, remains obscure.

Supplementary to the study of human cases of jaundice, an extensive survey was made to determine the presence of *L. icterohemorrhagiae* in wild rats. A leptospira was demonstrated in the kidneys of over 40 per cent, and immunologic tests of the rat serums indicated its presence in over 60 per cent of the rats captured in Albany.

The leptospira isolated from Albany rats is apparently identical in morphology, cultural reactions, pathogenic properties, and immunologic reactions with *L. icterohemorrhagiae.*

The pathogenicity of the rat leptospira for human beings, which had been assumed from the identity of the leptospira strains from rats and human cases, was directly demonstrated by a case of accidental human infection with the Albany rat leptospira.

A study of the immunologic reaction in this case indicated a close relationship of the rat leptospira to a strain of *L. icteroides* isolated by Noguchi from a case of yellow fever. Even four years after recovery, the serum of this patient gave marked protection to guinea-pigs against a highly virulent passage strain of *L. icteroides* as well as against *L. icterohemorrhagiae.* The serums of yellow fever convalescent patients studied by Noguchi, on the other hand, not only have failed to show a similar effect on *L. icterohemorrhagiae,* but have failed in some instances to protect guinea-pigs against yellow fever strains of icteroides.

AUTHORS' SUMMARY.

BRILLIANT GREEN AND ITS USE IN AN ENRICHMENT MEDIUM IN THE ISOLATION OF TYPHOID AND PARATYPHOID ORGANISMS. MORRIS L. RAKIETEN and LEO F. RETTGER, J. Infect. Dis. **41**:93, 1927.

The combined use of a buffered brilliant green enrichment medium and of a modified Endo agar is shown to be more satisfactory for the isolation of *Bacterium typhosum* than direct plating on Endo, eosin methylene blue, or brilliant green agar. The examinations included 204 artificially infected specimens, 50 unknown samples and 50 samples from patients with a clinical diagnosis of typhoid. The most favorable dilutions of brillant green range from 1 : 165,000 to 1 : 500,000. To the strong buffering agent—mixed phosphate solution—which prevents alkalinity which precipitates the billiant green, is attributed much of the success of this method. Grübler's brilliant green was found most reliable.

AUTHORS' SUMMARY.

COCCAL FORMS OF THE DIPHTHERIA BACILLUS. H. J. PARISH, Brit. J. Exper. Path. **8**:162, 1927.

From time to time coccal forms may appear in tryptic digest-broth cultures of *Bacillus diphtheriae.* These coccal forms are virulent and toxicogenic and do not appear to be in any sense degenerative.

NONTOXIC VARIANTS OF B. TETANI. PAUL FILDES, Brit. J. Exper. Path. **8**:219, 1927.

Confirmatory evidence is produced of the existence of nontoxic strains of *Bacillus tetani.* Such strains are regarded as variants from the "ideal" tetanus bacillus. In extreme examples of variation differentiation from related organisms is accomplished only by agglutination.

EXPERIMENTAL ORIENTAL SORE. G. PANJA, Indian M. Gaz. **62**:250, 1927.

A typical oriental sore in a man was produced by intradermal injection of a culture of *Leishmannia tropica* containing flagellate forms. The experimental sore was cured with carbon dioxide snow.

ON HEMOLYTIC STREPTOCOCCI AS SECONDARY INFECTORS IN PULMONARY TUBERCULOSIS: THEIR RELATIONSHIP TO THE INCIDENCE OF HEMOPTYSIS AND HECTIC FEVER. W. M. CUMMING, Tubercle **8**:308, 1927.

Of 119 patients with pulmonary tuberculosis, twenty-two had hemolytic streptococci in the sputum indistinguishable from those found in surgical practice. The occurrence of these organisms in the sputum was shown to be related to a limited extent with the incidence of hemoptysis and pyrexia and with the mortality. Eighty-nine patients had a streptococcus of the pseudohemolytic type in the sputum, markedly resembling the hemolyticus, but distinguished from it and from *Streptococcus viridans* by cultural and serologic methods. The occurrence of *Streptococcus pseudohemolyticus* in the sputum appears to have no prejudicial effect on the outlook of a case of pulmonary tuberculosis.

H. J. CORPER.

BOTRYOMYCOSIS: CONCERNING TWO CASES OF OSTEOMYELITIS CONTAINING BOTRYOMYCOTIC GRAINS. C. R. FUMAGALLI, Ann. d'anat. path. **4**:513, 1927.

Gumagali produces ample evidence to show that botryomycosis found in animals and in human beings is not due to a fungus related to actynomycosis but is caused by *Staphylococcus aureus*.

B. M. FRIED.

THE ANTECEDENTS OF PLEURITICS. F. BEZANÇON and M. P. WEIL, Ann. de med. **21**:266, 1927.

Serofibrinous pleurisy analogous to tuberculosis of the pulmonary parenchyma in the adult is the result of an infection which occurred in childhood. A careful history will reveal that the patient's "familial antecedents" are "loaded" with tuberculosis. The past history of the patient himself is usually unimportant. The negative past of the pleuritic patient impressed numerous observers with the fact that tuberculosis of the pleura is a primoinfection, which is erroneous. Persons with serofibrinous pleurisy have been infected previously, but their lesion due to Koch's bacillus was extrapulmonary or else it was a localized one, being confined to the supporting tissue of the lungs. Moreover, it was so small that it could not be disclosed either by physical examination or by roentgenograms. The sputum in the pleuritic patient is, as a rule, negative. Serofibrinous pleurisy usually follows a small infection with the tubercle bacillus.

B. M. FRIED.

COMPARATIVE STUDY OF SOME VIRUSES OF RECURRENT FEVER, PATHOGENIC FOR MAN. C. NICOLLE and C. ANDERSON, Arch. l'Inst. Pasteur de Tunis **16**: 123, 1927.

The authors have recorded in some detail their various studies of the virus of recurrent Spanish fever, of the bloody spirochetosis of the shrew, of the tick fever (Dutton) and of the North African recurrent fever. The pathogenicity toward various animals is recorded. Data on the immunity conferred by each virus against itself and against the other viruses are presented. Attempts to culture were made, but were not particularly successful. The spirochete of recurrent Spanish fever and la récurrente mondiale (North African) appear to the authors to be particular species. The spirochete of the tick and of the shrew fevers appeared to be identical. The paper, presented in eighty-three pages, is essentially a compilation of past and present work on spirochetes by these authors, and must be consulted for details.

M. S. MARSHALL.

THE EVOLUTION OF SPIROCHETE AND THE MECHANISM OF THE CRISES IN SPIROCHETOSIS. C. NICOLLE, Arch. l'Inst. Pasteur de Tunis **16**:207, 1927.

The author attempts to correlate three stages in the development of spirochetes with the crises and with the immunity in spirochetosis. The first stage, invisible (a "granulation" form), is without virulence, but represents the form of conservation or of resistance; the second, a "previsible" formed spirochete stage of a size too small to be seen, is the virulent form and the third is the typical adult spirochete deprived of virulence. The crisis occurs when the blood is invaded by "previsible" forms. Attention is called to certain analogies which may be drawn between the crises of spirochetoses and of other infectious diseases, as pneumonia.

M. S. MARSHALL.

PRIMARY MENINGITIS CAUSED BY MUMPS VIRUS. R. J. WEISSENBACH and others, Bull. et mém. Soc. méd. d. hôp. de Paris **57**:881, 1927.

The question whether primary meningitis may be caused by the virus of mumps is discussed on the basis of a case in which meningeal symptoms preceded a right parotitis. Three analogous cases are noted.

INFECTIOUSNESS OF SYPHILITIC CADAVER. E. ZURHELLE and R. STREMPEL, Arch. f. Dermat. u. Syph. **153**:219, 1927.

The possibility of infection with syphilis by the cadaver was demonstrated experimentally up to four days. The time would be longer in cadavers kept on ice, since decomposition tends to destroy the spirochetes. The virus may become attenuated and lead to symptomless infection, but the attenuation is not maintained in further inoculations.

ON THE REACTIVE PROCESS DURING THE DEVELOPMENT OF THE MILIARY TUBERCLE IN THE LIVER. H. SCHLEUSSING, Beitr. z. Klin. d. Tuberk. **65**:521, 1927.

This is a report of detailed studies on the histology and the histogenesis of hepatic tubercles, based on examinations of 200 cases. In close parallelism with other inflammatory diseases, three factors constitute the tissue alterations in tuberculosis, namely, tissue injury, circulatory disturbances and productive processes. The relative predominance of one or two factors, and variations in the chronologic sequence of the alterations account for the differences in various lesions. Tissue injury is always present and is always the inception of the process. It may be the only process noticeable in a lesion. The circulatory disturbances are characterized by exudation; the productive processes lead to formation of new tissue and encapsulation. The early exudative processes are believed to play an insignificant rôle in the further evolution of tubercles. Neither the proliferation of epithelial cells, nor the accumulation of hematogenous elements has any relation to epitheloid cells. Only processes in the vascular and connective tissue lead to a formation of the latter cell type and therewith to productive processes.

MAX PINNER.

AN ERYTHEMA PHENOMENON IN PULMONARY TUBERCULOSIS. C. ZAWISCH-OSSENITZ, Beitr. z. Klin. d. Tuberk. **65**:581, 1927.

After the thorax of children with pulmonary tuberculosis is rubbed with alcohol, red spots appear on the skin which represent a fair projection of the diseased parts of the pulmonary tissue. The size, shape and intensity of these spots coincide well with the clinical and roentgenologic observations. Only in hopeless cases is the erythema produced less than would be expected from the extent of the lesion. Fibrotic processes produce a weaker reaction than do exudative processes. This phenomenon could be elicited in all tuberculous children examined. Wrongly positive reactions were observed in children with a pronounced lability of the vascular system, in bronchitis and in bronchopneumonia. These pseudoreactions can easily be differentiated from the true reactions. Experiments on adults have not as yet been finished.

MAX PINNER.

ALTERATIONS IN THE ENDOCRINE SYSTEM OF THE PANCREAS UNDER THE INFLUENCE OF TUBERCULOUS TOXEMIA. O. S. KASARNOWSKAJA, Beitr. z. Klin. d. Tuberk. **65**:777, 1927.

In twelve cases of pulmonary tuberculosis the relative number of pancreatic islets were determined. It was found that the number of the Langerhans islets is increased in tuberculous patients. The relation of this observation to the previously reported observation, that the volume of the thyroid gland is decreased in tuberculosis, is discussed.

MAX PINNER.

BRONCHOSPIROCHETOSIS IN FOWLS. P. KRAGE and F. WEISGERBER, Centralbl. f. Bakteriol. **102**:60, 1927.

The authors describe the observations in a hen infected with a spirochete of *Treponema morsus-muris* type. There was a fibrinocellular inflammation of the bronchial and tracheal mucosa. Normally saprophytic, these organisms may become pathogenic.

PAUL R. CANNON.

LABORATORY INFECTION WITH CHOLERA. A. SATA, Deutsche med. Wchnschr. **53**:1052, 1927.

The laboratory infection is reported of a physician with the cholera vibrio, which had been isolated one and one-half years before.

A CASE OF INTRA-UTERINE TRANSMISSION OF RELAPSING FEVER. R. ADELHEIM, Jahrb. f. Kinderh. **114**:169, 1926.

A detailed postmortem report is made of a case of relapsing fever acquired in utero. The child was markedly icteric at birth and died on the seventh day. The icterus of the central parts of the brain ("Kernicterus") was the chief reason for the report. This condition is rare even in the most severe icterus, and the mechanism of its development is not well known. There were marked microscopic changes in the choroid plexus and in the ependyma, and these changes may render the structures described more permeable to bile pigments.

DOUBLE INFECTION WITH EXPERIMENTAL TUBERCULOSIS AND TRICHOPHYTOSIS. H. MARTENSTEIN and K. G. LEBERMANN, Klin. Wchnschr. **6**:299, 1927.

Guinea-pigs were inoculated intradermally with tubercle bacilli and the fungus of ringworm. Simultaneous inoculation did not have any effect on the course of either disease. In double inoculations with an interval of a week or more the primary disease was uninfluenced; the secondary was markedly changed. A tuberculosis produced after a trichophytosis was practically free from skin and gland manifestations.

J. D. WILLEMS.

ENDOTHELIAL CELLS IN SEPSIS. J. HAMMERSCHMIDT, Klin. Wchnschr. **6**:651, 1927.

A bacillus, extremely virulent for mice, did not cause any macroscopic changes of note, but all endothelial cells and the Kupffer cells were found filled with organisms.

CHANGE OF THE WATER SPIROCHETE INTO SPIROCHETA ICTEROGENES. R. UHLENHUTH and E. HERRMANN, Med. Klin. **23**:599, 1927.

Laprophytic spirochetes from water were changed into spirochetes typical of Weil's disease, by growth on medium containing rabbit or rat serum.

THE VITALITY OF SCARLATINAL STREPTOCOCCI. H. M. VON JETTMAR, Ztschr. f. Hyg. u. Infektionskr. **107**:265, 1927.

The author found hemolytic streptococci in 100 per cent of 120 cases of scarlatina. Pure cultures of them or mucus from the throat containing them were dried on cotton and kept in the dark at room temperature. Living streptococci could be obtained from this material for over one-half year. The floating dust scraped off from the pieces of cotton contained living fully virulent streptococci. Of the streptococcal flora from the mouth of patients with scarlet fever the hemolytic streptococci survive the drying longest, while those in the viridans group die within a few weeks. Hemolytic streptococci which have been in a dried condition for a long time at first show a retardation of growth on artificial culture medium which disappears rapidly. When tested on animals, they prove to be fully virulent. Their production of toxin also remains unaltered. Even exposure to direct sunlight and to other atmospheric influences for days does not destroy them. The results of the experiments demonstrate the great resistance of the scarlatinal streptococci and the possibility of infection by dry dust.

W. OPHÜLS.

THE RELATIONS BETWEEN THE RETICULO-ENDOTHELIAL SYSTEM AND CHEMOTHERAPEUTIC EFFECT. CLAUS W. JUNGEBLUT, Ztschr. f. Hyg. u. Infektionskr. **107**:357, 1927.

The investigations of Jungeblut tend to show that in mice in which the reticulo-endothelial system has been injured by blocking or extirpation of the spleen an infection with recurrens spirilla runs a more acute course than in normal animals. The mortality rises from 11 to 62 per cent. There is also some temporary interference in the establishment of an immunity in animals that survive the infection. Doses of neoarsphenamine which in normal mice abort the infection in 100 per cent of the animals are insufficient to produce the same effect in animals with an injured reticulo-endothelial system. The same reduction in chemotherapeutic effect is also noticed in mice infected with trypanosomes. Similarly the chemotherapeutic action of Bayer 205 on trypanosome infection was distinctly less efficient in mice with damaged reticulo-endothelial system. These observations suggest that in the animal body these chemotherapeutic agents are changed under the influence of the cells of the reticulo-endothelial system from a form which is inactive into a form which is actively destructive to the parasites.

W. OPHÜLS.

TUBERCULOUS INFECTION OF GUINEA-PIGS WITH MINIMAL DOSES OF BACILLI. WALTER LEVINTHAL, Ztschr. f. Hyg. u. Infektionskr. **107**:387, 1927.

The experiments seem to prove that guinea-pigs may succumb to an infection with one single tubercle bacillus.

W. OPHÜLS.

AGGLUTINATION ANALYSIS OF THE PARATYPHOID B GROUP (PARATYPHOID B SCHOTTMÜLLER AND MOUSE TYPHOID BACILLI). K. AOKI and G. TAKAYANAGI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:145, 1927.

The authors divide these organisms into two types, specific and nonspecific, and describe the detailed differences between them.

PAUL R. CANNON.

THE RELIABILITY OF CERTAIN BIOLOGIC AND SEROLOGIC TESTS FOR THE DIFFERENTIATION OF THE PARATYPHOID GROUP. KURT NUCK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:193, 1927.

Nuck has tested various methods for the differentiation of members of the paratyphoid group. He finds the raffinose reaction and the mucin formation

particularly useful, but could not confirm Müllers use of the gelatin slant, nor was the agglutination with the serums of different types of sufficient differentiating value.

PAUL R. CANNON.

THE SEROLOGIC TYPE DIFFERENTIATION OF THE PARATYPHOID B GROUP. Y. SHIIBA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:247, 1927.

Shiiba utilized the method of receptor analysis and found the results in general to correlate with the clinical picture. He found that the differences in agglutination between the paratyphoid B and the food-poisoning bacilli were too inconstant to serve as a diagnostic method.

PAUL R. CANNON.

THE CULTIVATION IN IMMUNE SERUM AS A METHOD FOR THE TYPE DIFFERENTIATION OF THE PARATYPHOID B GROUP. Y. SHIIBA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:267, 1927.

The growth in an immune serum broth proved to be a useful means of differentiating paratyphoid B from suipestifer bacilli, but for the type differentiation of paratyphoid B and food-poisoning strains it did not prove to be useful.

PAUL R. CANNON.

THE SEROLOGIC POSITION OF BACILLUS SUIPESTIFER. M. SHIBATA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:288, 1927.

By using strains of *Bacillus suipestifer* isolated from both sound and sick swine, which culturally reacted as paratyphoid B bacilli, and by absorption agglutination Shibata divided them into three groups: (*a*) food-poisoning type of the type of Breslau or Freiburg; (*b*) *Bacillus suipestifer* (confirmation of Manteufel and Beger) and (*c*) a few peculiar strains (paratyphosus C of Uhlenhuth and Hübener).

PAUL R. CANNON.

MY RESEARCHES IN TUBERCULOSIS DURING THE YEARS 1918 TO 1926. A. SATA, Ztschr. f. Tuberk. **48**:6, 1927.

The author gives a complete review of his studies in tuberculosis. The preparation of his immunizing vaccine, Vitaphthisin, is described. Virulent tubercle bacilli are slowly and completely dried and ground up over a period of not less than three months. Active immunization of animals with this bacillary powder produces in chronologic order the same changes in reactability of the body as does an infection. First, the animal acquires the ability to react against tubercle bacilli with an exudative inflammation. Later on it reacts with fibrotic proliferation. The exudative diathesis, present in the period immediately following the infection, is characterized by the ability of the tissues and the humours to decompose the specific toxin. The later causes an alteration of the tissue, particularly of the blood vessels, and consequently an acute exudation. In the next stage of immunity (tertiary stage) the fibrotic diathesis is developed. Instead of exudations, fibrous proliferation occurs at the site of tuberculous foci. These alterations are brought about by the resorbed antigens. An alterogenous and a fibrogenous antigen within the tubercle bacillus are distinguished. If animals are infected while they are in the first (exudative) stage of immunity, they die rapidly after developing acute serous and serofibrinous pleuritis and peritonitis. If the infections occur during the fibrogenous stage, the animals die after many months under the typical pathologic picture of human disease. Similar changes in the reaction of the animal body against infection can be brought about by previous infections with tubercle bacilli. It is concluded that this experimental work proves the contention that superinfection and reinfection with small amounts of tubercle bacilli early in life play an important rôle in the development of human phthisis in later life.

MAX PINNER.

THERAPY BY METAL SALTS. STERILIZATION OF THE INFECTED ORGANISM. L. E. WALBUM, Ztschr. f. Tuberk. **48**:193, 1927.

In continuation of previously reported work, experiments are reported to show that infected animals can be completely sterilized by the administration of certain salts in optimal concentration. Mice infected with virulent spores of tetanus bacilli can be sterilized with manganese salts. The spores are deprived of their virulence before they are completely destroyed. When rabbits infected intravenously with virulent tubercle bacilli are treated with optimal amounts of manganese, cerium, lanthan or cadmium salts starting seven days after the infection, it is possible to prevent the development of tuberculous disease. If the treatment is started thirty-three days after the infection, the animals can be completely healed of tuberculosis. That in this case a cure of an individual with an actual and well developed disease is affected, is proved by the fact that some of the control animals died at the time when treatment was started with extensive tuberculous disease. The results in experimental tuberculosis in guinea-pigs were less definite, although encouraging. Mice infected with tubercle bacilli could be completely sterilized with optimal amounts of manganese salts.

MAX PINNER.

ON PRESENT KNOWLEDGE CONCERNING CORPUSCULAR FORMATIONS IN EXPERIMENTAL AND EPIZOOTIC ENCEPHALITIS. CARL KLING, Finska läk-sällsk. handl. **69**:563, 1927.

After a review of the observations on herpes-encephalitic virus (Levaditi-Harvier), and the so-called Swedish encephalitic virus, as well as on the formations named *Encephalitozoon cuniculi*, Kling emphasizes that it is not possible, on morphologic grounds, to identify epizootic encephalitis in rabbits with the encephalitis that is produced by the inoculation of rabbits with human encephalitic material. Does it concern two separate infections? It is pointed out that up to the present the human material subjected to examination has been obtained from relatively acute cases of the disease; only a few cases of chronic epidemic encephalitis have been examined carefully. Such cases should be examined with particular reference to the presence of corpuscular elements. It is suggested that the reaction in the rabbit may differ from that of man to the virus of epidemic encephalitis, the cause of which is still unknown.

THE BACTERIOPHAGE IN THE TREATMENT OF BACILLARY DYSENTERY OF THE FLEXNER TYPE. WILLIAM FLETCHER and K. KANAGARAYER, Bulletins from The Institute for Medical Research, Kuala Lumpur, Federated Malay States, no. 3, 1927.

A supply of the bacteriophage was received from Dr. F. d'Herelle. The majority of the deaths from dysentery in the Malay States are due to organisms of the Flexner group; infections with Shiga's bacillus are uncommon. The bacteriophage was administered to twenty-two men suffering from dysentery caused by bacilli of the Flexner group. A bacteriologic examination of their feces was made every day. Dysentery bacilli persisted in the feces of six patients for more than ten days after the beginning of treatment. In eleven cases, the bacilli were found up to the sixth day but not after the eighth. In the remaining five cases they were not found after the fourth day. Three patients died during treatment; healthy dysentery bacilli were isolated from their intestines after death. The organisms isolated from the feces of these twenty-two patients, and from the intestines of the fatal cases, had the usual features of normal dysentery bacilli, in appearance, growth, agglutination and carbohydrate reactions. The action of the bacteriophage on Andrewes' type strains was tested in vitro. It was rather more virulent for these than for freshly isolated strains. When the bacteriophage was added to broth cultures of freshly isolated dysentery bacilli, a few organisms survived in each case.

but the resulting "mixed cultures" had little vitality, as a rule; and they were generally nonagglutinable by specific serums. Only a single case of dysentery due to Shiga's bacillus was available for treatment with the bacteriophage. In this instance, dysentery bacilli were not isolated after the second day of treatment. The action of the bacteriophage on Shiga's bacillus, in vitro, was much stronger than its action on organisms of the Flexner group.

AUTHORS' SUMMARY.

Immunology

RESPIRATORY ANAPHYLAXIS. BRET RATNER, H. C. JACKSON and HELEN LEE GRUEHL, Am. J. Dis. Child. **34**:23, 1927.

The authors were able to induce sensitization to horse dander in guinea-pigs by injecting dander extract, allowing a suitable incubation period to elapse and giving inhalations of the dried substance. Animals so sensitized showed anaphylactic reaction similar to asthma in man.

RUTH E. TAYLOR.

THE PROTECTIVE AND CURATIVE ACTION OF LARGE DOSES OF PNEUMOCOCCUS ANTISERUM IN MICE. FRANCES A. COVENTRY, Am. J. Hyg. **7**:515, 1927.

Samples of the blood of mice treated with antiserum I were plated at intervals. The survival of the mice was found to be correlated with the appearance of pneumococci in the peripheral blood.

HEPARIN INHIBITION OF ANAPHYLACTIC SHOCK. ROSCOE R. HYDE, Am. J. Hyg. **7**:614, 1927.

Intravenous injections of heparin in amounts sufficient to inhibit the coagulation of the total blood volume of a guinea-pig do not inhibit a fatal issue in the anaphylactic guinea-pig. Neither does heparin inhibit the deaths from primary toxicity in guinea-pigs that follow intravenous injections of fresh ox serum, immune heterophil serum or histamine. Heparin does inhibit death in the rabbit due to intravenous injections of tissue extracts.

AUTHOR'S SUMMARY.

THE COMPLEMENT-DEFICIENT GUINEA-PIG. A STUDY OF AN INHERITED BIOCHEMICAL STRUCTURE IN RELATION TO A TOXIC IMMUNE BODY. ROSCOE R. HYDE, Am. J. Hyg. **7**:619, 1927.

Immune hemolytic serums of heterophil type, antichicken and antisheep rabbit serums, are nontoxic for the complement deficient guinea-pig in amounts that kill the normal guinea-pig on intravenous injection and give rise to necrosis on cutaneous injection. The behavior of the deficient guinea-pig toward the heterophil serums is not explicable in terms of complement as such, since those animals whose blood stream has been activated by intravenous injections of human serum escape the toxic action of the heterophils serums as shown by intravenous and cutaneous tests. Guinea-pigs that are deficient in complement are subject to anaphylactic shock and are susceptible to a toxic action of adult beef serum and of virulent diphtheria cultures in the same manner as the normal guinea-pig.

RESPIRATORY IMMUNITY IN RABBITS. INTRANASAL INFECTION AND IMMUNIZATION WITH PNEUMOCOCCI. CARROLL G. BULL and C. M. MCKEE, Am. J. Hyg. **7**: 627, 1927.

Rabbits are susceptible to infection with pneumococci by intranasal inoculation. Depending on the virulence of the culture, intranasal inoculation may cause: (1) no signs of infection; (2) a transient infection with positive blood culture and marked temperature reaction from which the rabbit fully recovers, and (3) acutely fatal septicemic infection without temperature reaction or

leukocytosis. Rabbits that have recovered from an infection or that have been immunized with pneumococci in any way are resistant to infection by the nasal route, apparently regardless of the virulence or the amount of culture used. Rabbits often develop antibodies following intranasal inoculation without having shown any signs of infection. These are also resistant to infection by this route. It has been observed that rabbits may develop the capacity to react successfully to infection with virulent pneumococci as the result of an intranasal inoculation which did not cause detectable reaction or antibody production. These rabbits react to virulent cultures as normal rabbits do to avirulent cultures.

AUTHORS' SUMMARY.

A METHOD FOR DETERMINING THE ANTI-PNEUMOCOCCAL PROPERTIES OF WHOLE BLOOD AND THE PROTECTIVE POWER OF IMMUNE SERUM. CARROLL G. BULL and SHAN MING TAO, Am. J. Hyg. **7**:648, 1927.

A simple method for testing the pneumococcidal power of whole blood has been described. Coagulation of the blood is prevented by adding 1 per cent by volume of a saturated solution of sodium citrate. The antipneumococcal titer of the citrated blood is determined by adding varying quantities of pneumococcus culture to measured quantities of the blood. The power of the citrated blood to resist the growth of pneumococci parallels the resistance of the animal to infection with these organisms. For example, it takes more than 1,000,000 times as many pneumococci to infect 0.5 cc. of chicken blood as it does to infect the same amount of normal rabbit blood. Normal rabbit blood can be rendered resistant to infection with pneumococci by the addition of anti-pneumococcus serum. The power of the immune serum to protect the susceptible blood seems to be directly related to its power to protect mice against infection. This may be of service in the standardization of therapeutic serums. The growth of pneumococci under these conditions was followed by noting the changes in the color of the blood and by the examination of stain smears.

MUCOUS COLITIS DUE TO FOOD ALLERGY, WITH A REPORT OF FIVE CASES. EDWARD HOLLANDER, Am. J. M. Sc. **174**:495, 1927.

Five cases are presented in which food allergy was the cause of mucous colitis. The symptoms and objective manifestations disappeared following the withdrawal of foods to which the patients were sensitized, and could be made to reappear by their ingestion.

AUTHOR'S SUMMARY.

THE HEMOLYTIC, CYTOLYTIC AND COMPLEMENT-BINDING PROPERTIES OF EXTRACTS OF ENDAMOEBA HISTOLYTICA. CHARLES F. CRAIG, Am. J. Trop. Med. **7**: 225, 1927.

There were present in the absolute alcohol extracts of 48 hour old cultures of *Endamoeba histolytica* hemolytic, cytolytic and complement-binding substances. The hemolytic properties of such extracts were destroyed by heating the extracts to 80 C. in a water bath for one hour. The hemolytic substance was soluble in absolute alcohol and practically insoluble in normal salt solution. The hemolytic substance was not an exotoxin, as it was not present in the supernatant fluid of cultures of *Endamoeba histolytica*. The hemolytic agent was only present in the living organism, as extracts of old cultures not containing living amebas did not possess hemolytic properties. The hemolytic agent was not specific for human red blood corpuscles but was equally hemolytic to erythrocytes of rabbits and guinea-pigs. The extracts did not contain any bacteriolytic substance. The complement-fixing substance contained in the extracts was apparently specific for *Endamoeba histolytica* to the blood serums of persons harboring other amebas giving negative results with these extracts.

AUTHOR'S SUMMARY.

LENS PROTEIN. ALAN C. WOODS and EARL L. BURKY, J. A. M. A. **89**:102, 1927.

By using the iso-electric points of alpha and beta crystallins, these have been obtained as pure and distinct antigenic substances. The beta crystallin tends to precipitate within the hydrogen ion range of the fluids of the body, but this precipitation is prevented by the presence of alpha crystallin. It is suggested that these observations may have a bearing on the explanation of senile cataract.

STAPHYLOCOCCUS EXOTOXIN. I. PILOT and M. L. AFREMOW, J. A. M. A. **89**:939, 1927.

The production of exotoxin by *Staphylococcus aureus*, demonstrated by Parker, is confirmed. Sterile filtrates cause in man a skin reaction that is neutralized by the serum of rabbits and horses immunized with the filtrates.

IMMUNOLOGICAL PROPERTIES OF A TYPICAL (S-PRODUCING) AND A DEGRADED (NON-S. PRODUCING) STRAIN OF TYPE II PNEUMOCOCCUS, WITH SPECIAL REFERENCE TO PROTECTIVE ANTIBODIES. EMIDIO L. GASPARI, WILLIAM L. FLEMING and JAMES M. NEILL, J. Exper. Med. **46**:101, 1927.

The loss of the specialized function of S production by type II pneumococcus was accompanied by a loss of the antigenic properties involved in both active and passive protection of mice. Absorption of type II serum with S-producing pneumococci removed all the protective antibodies, as well as the type-specific agglutinins and S precipitans. The same absorption treatment of the serum by non-S-producing pneumococci failed entirely to remove the type-specific antibodies and did not affect the protective value of the serum. Absorption with bacteria-free culture fluids containing the reactive carbohydrate removed the protective antibodies as completely as absorption with the whole bacterial cells of type-specific strains. The results taken as a whole indicate that the antibodies involved in the usual protection of mice against type II pneumococci are closely related, if not identical, to the specific anti-carbohydrate precipitin.

AUTHORS' SUMMARY.

FACTORS INVOLVED IN THE INFECTION OF MICE AFTER VACCINATION WITH TYPE II PNEUMOCOCCI. JAMES M. NEILL and EMIDIO L. GASPARI, J. Exper. Med. **46**:113, 1927.

A group of mice was vaccinated against type II pneumococci and subsequently tested for immunity against different numbers of the live bacteria. The immunity tests were conducted within two zones of dosage. In the first zone, in which the doses were kept within reasonable limits (10^{-4} to 10^{-5} cc. of culture), the number of invading bacteria was without influence and the occurrence of infections was determined by the previous immunity response of the individual. In the second zone of dosage (in which passive protection also fails), these relations were reversed, and invasion by overwhelming numbers of the bacteria invariably produced infection regardless of the previous immunity response of the individual. These results present an extreme example of the importance of the immunity response of the individual as a factor always concerned in the effectiveness of vaccination.

AUTHORS' SUMMARY.

IMMUNOLOGICAL SIGNIFICANCE OF MUTATIONS OF PATHOGENIC B. COLI FROM BOVINE SOURCES. THEOBALD SMITH and GLADYS BRYANT, J. Exper. Med. **46**:133, 1927.

On agar plates, certain strains of *B. coli* from the ileum of calves suffering from diarrhea or scours promptly mutate and give rise to forms which have lost capsular substance, whose virulence has been greatly reduced, and which have gained greatly in agglutinability and in being taken up by leukocytes. The original characters are not regained in cultures kept in the cold after

development, nor in rapid transfers in bouillon nor in passages through the peritoneal cavity of guinea-pigs. Filtrates of 48 hour bouillon cultures contain as much toxin in the (b) as in the (a) form, indicating no loss in this function.

AUTHORS' SUMMARY.

NORMAL AND SEROLOGICALLY INDUCED RESISTANCE TO B. COLI AND ITS MUTANT. THEOBALD SMITH, J. Exper. Med. **46**:141, 1927.

The interrelations between bacterial toxins, bacterial capsular (mucoid, viscid) substance and certain normal protective factors in the guinea-pig are studied with the aid of bacterial mutants and immune serum, and the results formulated in an hypothesis.

AUTHOR'S SUMMARY.

BIOCHEMICAL STUDY OF THE CAPSULAR SUBSTANCE OF PATHOGENIC B. COLI FROM BOVINE SOURCES. DOROTHEA E. SMITH, J. Exper. Med. **46**:155, 1927.

The soluble specific substance obtained from a capsulated strain of *B. coli* is not identical with any specific substance heretofore described. It is a carbohydrate, composed of 80 per cent of hexose, probably partly of dextrorotatory and partly of levorotatory sugar, since the rotation of the hydrolysate is low. Glucuronic acid is probably present in the molecule. Crude "residue" or specific substance obtained from the uncapsulated mutant was about 100 times less active with homologous serum than similar material from the capsulated strain. This supports the view that capsular substance and soluble specific substance are the same. In cases in which there is a well marked capsule, the specific substance is probably produced in greater amount and located peripherally. Capsular substance is probably significant for virulence when functioning as a morphologic capsule. It is present in filtrates of young culture only in small amounts.

AUTHOR'S SUMMARY.

ON THE MECHANISM OF THE SERUM SENSITIZATION OF ACIDFAST BACTERIA. STUART MUDD and EMILY B. H. MUDD, J. Exper. Med. **46**:173, 1927.

Sensitized acid-fast bacteria, as compared with untreated organisms, have an increased resistance to wetting with oil when tested at a saline-tricaprylin interface, and an increased cohesiveness as revealed both in the interface reaction and by the resuspension test (the clumping of thoroughly washed sensitized organisms resuspended in salt solution). These reactions, and related behavior in direct agglutination and complement fixation, are considered the result of a coating, with globulin from the antiserum, over the antigenic alcohol-soluble material of the bacterial surface (possibly conjugated lipins owing their specificity to carbohydrate haptins). The action of immune serums apparently differs only quantitatively, not qualitatively, from that of various normal serums. The prezone is attributed to a too high concentration of colloids, and does not appear in the resuspension test. Antipneumococcus globulin from horse serum (Felton), tested at the saline-tricaprylin interface before and after boiling, showed after this denaturation an increased resistance to wetting by oil indistinguishable from the behavior of sensitized acid-fast bacteria, and strengthened the evidence that the sensitized bacteria are coated with denatured globulin.

EXPERIMENTS IN IMMUNIZATION WITH LECITHIN. P. A. LEVENE, K. LANDSTEINER and J. VAN DER SATREER, J. Exper. Med. **46**:197, 1927.

Serum immune against lecithin from egg (Merck) did not react with lecithins prepared by the authors. Several explanations of these results suggest themselves, one being that there may be a special substance present in active lecithin preparations. Further results must be awaited.

ON A SPECIFIC SUBSTANCE OF THE CHOLERA VIBRIO. K. LANDSTEINER and PHILIP LEVENE, J. Exper. Med. **46**:213, 1927.

Specific substances have been extracted from *V. cholerae* by hot dilute alcohol, which contain a precipitable or nonimmunizing, nonprotein, sugar-containing substance, and an antigenic protein.

REINOCULATION OF TREATED AND UNTREATED SYPHILITIC RABBITS WITH HETEROLOGOUS STRAINS OF TREPONEMA PALLIDUM. ALAN M. CHESNEY, CHARLES R. L. HALLEY and JAROLD E. KEMP, J. Exper. Med. **46**:223, 1927.

The resistance developed in rabbits during a syphilitic infection is strain-specific rather than species-specific.

THE RELATION OF OPSONINS TO NATURAL RESISTANCE AGAINST PNEUMOCOCCUS INFECTION. OSWALD H. ROBERTSON and RICHARD H. P. SIA, J. Exper. Med. **46**:239, 1927.

The serum of animals (dog, cat, sheep, pig and horse) resistant to the pneumococcus renders virulent pneumococci phagocytable by homologous and other leukocytes. The serum of animals suspectible to the pneumococcus does not have such an effect.

THE "REACTIVATION" OF THE BACTERIOLYTIC ACTIVITY OF OXIDIZED PNEUMOCOCCUS EXTRACTS. JAMES M. NEILL and WILLIAM L. FLEMING, J. Exper. Med. **46**: 263, 1927.

The methods previously employed in the study of hemotoxins have been applied in the present investigation to the oxidation and reduction of the bacteriolytic substance of *Pneumococcus*. It is shown that the bacteriolytic agent, previously inactivated by oxidation, can be "reactivated" by treatment with bacterial reducing agents. Evidence is presented that this "reactivation" represents the reduction of inactive, reversible oxidation products to the original active substance. The bacteriolytic agent is an integral constituent of the pneumococcus cell, which can be separated from the hemotoxin by absorption with red blood cells in the cold.

AUTHORS' SUMMARY.

THE DIFFERENTIATION OF TETANOLYSIN AND TETANOSPASMIN. WILLIAM L. FLEMING, J. Exper. Med. **46**:279, 1927.

Tetanolysin and tetanospasmin possess in common the immunologic properties of the group of "antitoxinogens." Both of them are contained in undeteriorated culture fluids of the tetanus bacillus, but each of them represents a distinct and separate antigenic substance. Experimental data illustrating points of difference in their properties are presented in this paper.

AUTHOR'S SUMMARY.

THE EFFECT OF HEAT ON ANTIBODIES. F. S. JONES, J. Exper. Med. **46**:291, 1927.

Logarithmic curves are presented showing the behavior of various antibodies under various conditions of heat.

AGGLUTINATION BY PRECIPITIN. F. S. JONES, J. Exper. Med. **46**:303, 1927.

Serum (antigen) when heated at a temperature sufficient to cause definite clouding reacts more intensely with a specific precipitin than a portion of the unheated serum or samples heated at lower temperatures. The phenomenon is explained on the basis that coagulated protein in suspension is covered with undenatured antigen and the addition of precipitin causes agglutination of the coagulated protein. Similar phenomena are obtained when bacteria or collodion particles are mixed with diluted serum (antigen) and precipitin

added; the particles or bacteria agglutinate and increase the visibility of the reaction. Further, it is shown that collodion particles sensitized with cow serum or crystallized egg albumin and subsequently washed until the washing fluid no longer contains the antigenic substance will agglutinate when small quantities of specific precipitin are added. Bacteria sensitized with cow serum and subsequently washed until cow serum no longer remains in the washing solution, agglutinate when cow antiserum at fairly low concentration is added. It was not possible to show that bacteria soaked in crystallized egg albumin and subsequently washed retained on their surfaces sufficient undenatured egg albumin to react to crystallized egg albumin precipitin.

AUTHOR'S SUMMARY.

STUDIES ON IMMUNITY TO PNEUMOCOCCUS MUCOSUS (TYPE III): III. INCREASED RESISTANCE TO TYPE III INFECTION INDUCED IN RABBITS BY IMMUNIZATION WITH R AND S FORMS OF PNEUMOCOCCUS. WILLIAM S. TILLETT, J. Exper. Med. **46**:343, 1927.

Increased resistance against virulent type III pneumococci may be stimulated in rabbits by repeated injections of heat-killed cultures of homologous or heterologous pneumococci. This form of active immunity, effective in the absence of demonstrable type-specific antibodies and unrelated to the variety of the pneumococcus used for immunization, is considered dependent on an exaltation of the same factors which afford normal rabbits natural resistance to type III pneumococcus.

AUTHOR'S SUMMARY.

LOCAL SPECIFIC THERAPY OF EXPERIMENTAL PNEUMOCOCCAL MENINGITIS. FRED W. STEWART, J. Exper. Med. **46**:391 and 409, 1927.

In rabbits treatment by intrathecal serum causes rapid agglutination and phagocytosis of pneumococci, but cure very rarely follows this treatment. In dogs fibrinopurulent meningitis following intracisternal injection of virulent pneumococci of type I may be cured by lavage and introduction of optochin-serum mixtures.

ALLERGIC REACTIONS WITH STREPTOCOCCAL STRAINS FROM ERYSIPELAS. A. R. DOCHEZ and F. A. STEVENS, J. Exper. Med. **46**:487, 1927.

Rabbits immunized with culture filtrates of erysipelas streptococci show cutaneous allergy. Apparently the rash in scarlet fever and the Dick reaction are allergic reactions to products of *Streptococcus scarlatinae*.

THE SOLUBLE SPECIFIC SUBSTANCE OF FRIEDLÄNDER'S BACILLUS: III. ON THE ISOLATION AND PROPERTIES OF THE SPECIFIC CARBOHYDRATES FROM TYPES A AND C FRIEDLÄNDER BACILLUS. WALTHER F. GOEBEL and OSWALD T. AVERY, J. Exper. Med. **46**:601, 1927.

Strains of Friedländer's bacillus of types A and C yield, on fractionation, two chemically distinct nitrogen-free polysaccharids with highly specific properties. Both are strong acids and both contain glycuronic acid, or an isomer, within their molecules as shown by the napthoresorcinol test. The polysaccharids themselves are nonreducing, but on hydrolysis with mineral acids they yield reducing sugars. In both instances, as in the case of the pneumococci, specific function and carbohydrate apparently are inseparable. On comparing the specific carbohydrates from type B and type C, of Friedländer's bacillus, an unusual similarity in properties is to be observed. These substances, however, possess two distinct differences. Immunologically, they show no cross-relationship. Their solubility in water in the pure state and their whole behavior during purification are entirely different. In pure form the type B substance is difficultly soluble in water whereas the type C substance is readily soluble. The type B carbohydrate may be readily precipitated by

alcohol in the presence of hydrochloric acid. The type C substance, on the other hand, precipitates completely only after standing at 0 C. for an hour or more. The fact that two substances so alike in physical properties are totally dissimilar in immunologic reactions, may possibly be explained on the basis of slight differences in the intramolecular linkages of sugar to sugar, or of sugar to sugar acid.

THE RÔLE OF THE RETICULO-ENDOTHELIAL SYSTEM IN IMMUNITY: IV. THE ACTION OF DIPHTHERIA TOXIN IN SPLENECTOMIZED AND BLOCKED MICE. C. W. JUNGEBLUT, J. Exper. Med. **46**:609, 1927.

The minimum amount of diphtheria toxin which killed normal mice of from 24 to 30 Gm. in weight, on intravenous injection, was found to be between seventy-five and one hundred times the minimum lethal dose for the guinea-pig. When given intraperitoneally, the fatal dose for mice was as high as two hundred times the minimum lethal dose. There was no significant difference in the lethal action of diphtheria toxin for normal mice and mice in which an elimination of the reticulo-endothelial system had been attempted by means of blocking injections of India ink, or splenectomy, or a combination of both operations. Attempts to infect normal mice and mice treated as described with large doses of a highly virulent diphtheria strain were unsuccessful with both groups of animals.

AUTHOR'S SUMMARY.

A PRECIPITIN TEST IN MALARIA. WILLIAM H. TALIAFERRO, LUCY GRAVES TALIAFERRO and ANNA B. FISHER, J. Prev. Med. **1**:5, 1927.

In a series of 1,605 precipitin tests on the serums of 535 persons (295 with malarial parasites in the peripheral blood, 174 negative and sixty doubtful) with thirty-seven different antigens the following preliminary conclusions are indicated: The best antigen was prepared from a heavily infected placenta by mincing in a meat chopper, extracting with ether, digesting the ether insoluble portion in the slightly alkaline solution of coca and using the clear filtrate as antigen. When tested with serums from fifty-four infected persons, forty-five gave positive test (10 +++, 21 ++, 14 +) and two a doubtful positive; seven were negative. When tested against the serum of thirty-two persons showing a negative thick film for malaria, six gave a positive test (2 ++, 4 +) and one a doubtful positive; twenty-five were negative. Some results indicate that efficient antigens can be prepared from infected red blood cells provided they have a preliminary extraction with ether. All of the data indicate that the precipitation is a specific antigen-antibody reaction and not a nonspecific flocculation.

AUTHORS' SUMMARY.

ENZYME THEORY OF ANTIBODY FORMATION. W. H. MANWARING, Scientific Monthly, October, 1927, p. 362.

The enzyme theory is advocated as the most promising working hypothesis of the immediate physiologic mechanism of antibody formation. The same subject is discussed by the same author in the *J. Immunology* **12**:177, 1926.

A METHOD FOR DETERMINING THE FATE OF TUBERCLE BACILLI IMPLANTED IN HUMAN PLASMA. R. G. BANNERMAN, Brit. J. Exper. Path. **8**:209, 1927.

The observation that tubercle bacilli grow better in normal plasma than in that of tuberculous subjects has been confirmed.

DEVELOPMENT BY BACTERIA OF RESISTANCE TO LYSOZYME ACTION. A. FLEMING and V. D. ALLISON, Brit. J. Exper. Path. **8**:214, 1927.

Bacteria grown in contact with tissues or secretions are rendered comparatively resistant to their antibacterial action, but this resistance is not specific.

KINETICS OF HEMOLYSIS. ERIC PONDER and D. G. S. MCLACHLAN, Brit. J. Exper. Path. **8**:267, 1927.

So far as the kinetics of the fundamental reaction are concerned, the hemolytic action of the lysis of bacterial origin is identical with that of saponin and the simple hemolysis. The cells of different species offer to the action of the bacterial hemolysis very much the same resistance, such differences as can be found being exceedingly small.

PASSIVE IMMUNITY IN TETANUS BY CUTANEOUS ROUTE. A. BESREDKA and S. NAKAGAW, Ann. de l'Inst. Pasteur **41**:607, 1927.

Tetanus antitoxin applied to the shaved skin of guinea-pigs twenty-four hours before a fatal dose of toxin protects the animal. Applied from one to three hours after the toxin the same protection is afforded with occasionally more or less severe local toxic reactions. This protection is local. If, however, the serum is applied as a cream there is further penetration and protection against toxin injected at a distance. Antitoxin thus applied does not sensitize the animal and anaphylaxis will not occur.

G. B. RHODES.

VACCINATION AGAINST ANTHRAX BY ONE INTRADERMAL INJECTION. H. VELU, Ann. de l'Inst. Pasteur **41**:615, 1927.

Experimental and practical results with the single intradermal vaccination of large numbers of cattle, sheep, horses, hogs and laboratory animals prove this a simple and efficacious method and of superior economic value.

G. B. RHODES.

TETANUS ANATOXIN AND ACTIVE IMMUNIZATION OF MAN AGAINST TETANUS. C. RAMON and C. ZOELLER, Ann. de l'Inst. Pasteur **41**:803, 1927.

Ramon and his co-workers report success with a formalinized tetanus toxin or anatoxin, antigenically active but innocuous. An immunity lasting at least eighteen months was observed. The material may be used in connection with serum in urgent potential cases, or as a means of systematic immunization, as of mothers before the birth of their child, protecting both mother and child. Further specialized treatment of the subject is given in other articles in the same number of the *Annales de l'Institut Pasteur.*

MAX P. MARSHALL.

THE BIOLOGIC DIFFERENCE BETWEEN THE UNALTERED AND THE BOILED ANTIGEN IN TUBERCLE BACILLI. Y. IMAMAKI, Beitr. z. Klin. d. Tuberk. **65**:570, 1927.

Tubercle bacilli, as other bacillary antigens, decrease the spontaneous phagocytosis of pneumococci. This property can be destroyed by heating the antigen to 100 F. during from thirty to sixty minutes. Antigen treated in this way increases the normal amount of phagocytosis. The stimulating action is lost if the boiling is prolonged to two hours. The unaltered antigens do not only inhibit phagocytosis, but the fixation of antibody and complement as well. Boiled antigens have no such inhibiting actions and are, therefore, more desirable for therapeutic uses.

MAX PINNER.

HEMOLYSIS OF INCOMPLETELY FIXED ERYTHROCYTES. E. ECKSTEIN, Beitr. z. Path. Anat. u. z. allg. Pathol. **77**:342, 1927.

If erythrocytes which have been incompletely fixed by formaldehyde are subjected to alternate freezing and thawing, hemolysis occurs but is delayed, the rate of hemolysis being influenced by the temperature and by the degree of fixation.

O. T. SCHULTZ.

Tumors

CERTAIN CLINICAL AND PATHOLOGIC ASPECTS OF LYMPHOSARCOMA. DOUGLAS SYMMERS, Am. J. M. Sc. **174**:9, 1927.

Lymphosarcoma may implicate any of the lymphoid depots alone. It may bring about a diversified series of changes affecting tissues, lymphoid or otherwise, within more or less restricted territorial confines, or it may spread to include lymphoid and other structures over a wide geographic expanse. Lymphosarcoma displays a predilection for the lymphoid tissues of the gastro-intestinal tract, after which it seems to prefer the thymic remains as a place of operation. In the gastro-intestinal tract, its activities are comparatively mild. If it originates in the lymphoid remnants of the thymus, however, it is apt to bring about frightful destruction of contiguous tissues, featured by invasion of the pericardium and heart, by infiltration of the pleura and direct incursion into the lungs, by displacement of such mobile structures as the trachea, esophagus, aorta, pulmonary artery and vena cava, and sometimes by entrance into their walls, by penetration of the intercostal muscles and diaphragm, and finally by involvement of the regional or remote lymph nodes, or both. It is an astounding, if ominous, fact that in these circumstances, the changes enumerated may stretch themselves over an extended period without eliciting any complaint from the patient, and that both subjective and objective disturbances may be registered suddenly and without warning at a time when anatomic expansion has advanced beyond all hope of control. Although from the clinical point of view lymphosarcoma bears an intimate resemblance to a number of other conditions affecting the lymphoid system, among them chronic lymphatic leukemia, pseudoleukemia, certain forms of tuberculosis of the lymph nodes and follicular lymphadenopathy with splenomegaly, Hodgkin's disease offers perhaps the widest range of similarities. While it is true that lymphosarcoma, notably its gastro-intestinal forms, is capable of producing lesions that are unknown in Hodgkin's disease, in many other respects the two may impersonate one another to the minutest detail. Differentiation is to be accomplished only on the basis of excision and histologic examination of diseased tissue. Even in these circumstances confusion is possible, since in both conditions the initial changes in the lymph nodes are to be found in simple, diffuse hyperplasia of the lymphoid cells, the nodes in Hodgkin's granuloma later assuming the complex histologic picture by which the fully established disease may be identified with certainty.

AUTHOR'S SUMMARY.

PRIMARY CARCINOMA OF THE LUNGS. FURTHER STUDY, WITH PARTICULAR ATTENTION TO INCIDENCE, DIAGNOSIS AND METASTASES TO THE CENTRAL NERVOUS SYSTEM. B. M. FRIED, Arch. Int. Med. **40**:340, 1927.

The European literature contains statistics to the effect that the incidence of primary carcinoma of the lungs in relation to epithelial malignant disease in general is disproportionately high; figures given indicate that it occurs there in from 5 to 6 per cent of all postmortem examinations. In this country, similarly, an increase in the occurrence of primary carcinoma of the lungs has been noted in the last decade. Primary carcinoma of the lungs owes its statistical increase to (*a*) better diagnostic methods and (*b*) increased human longevity. The increase, therefore, is more apparent than real. A diagnosis of primary carcinoma of the lungs based on physical signs alone is never certain. Careful analysis of physical signs, combined with clinical observation and laboratory methods of investigation (roentgen rays, injection of iodized oil and bronchoscopy), makes the diagnosis of primary carcinoma of the lungs reasonably certain. Bronchoscopy, with removal of the tissue, is apparently the most reliable criterion. The wide distribution of metastases in primary carcinoma of the lungs is due to: (*a*) peculiarities of its structure, i. e., it is frequently soft and abundantly cellular, and (*b*) its slow growth,

since rapidly growing tumors usually cause death of the patient long before metastases have time to develop. The frequent occurrence of cerebral metastases from primary pulmonary cancer, as compared with cancers from elsewhere in the body, is due to the absence of a barrier between the lungs and the brain. Metastases from elsewhere in the body on their way to the central nervous system pass primarily through the "sieve" of the lungs, in which they are usually "immured" and not infrequently perish. Metastases to the brain from a primary pulmonary cancer are, as a rule, hematogenous in character.

AUTHOR'S SUMMARY.

FURTHER STUDIES OF THE TRANSPLANTATION OF THE LARVAE OF TAENIA CRASSICOLLIS AND THE EXPERIMENTAL PRODUCTION OF SUBCUTANEOUS CYSTICERCUS SARCOMATA. F. D. BULLOCK and M. R. CURTIS, J. Cancer Research **10**:393, 1926.

At an early stage of development, *Taenia* larvae stimulate the mesothelial cells of the liver or groin of rats or mice to active cell proliferation. This activity gradually subsides, but the cells differentiate into a fibrous cyst wall around the parasite. In the rat, at least, such cyst walls either in the liver or groin may undergo sarcomatous transformation.

Slightly older *Taenia* larvae surrounded by rudimentary or early fibrous cyst walls may be transplanted from the liver of the rat to the groins of rats or mice. The larvae continue to develop at about their normal rate and remain constantly surrounded by cyst walls but do not reproduce the characteristic cell proliferation in the new host. The walls of these groin cysts resemble the walls of the cysts of about the same age in the liver or those formed in the groin around larvae transplanted before encystment. Whether or not the cells of the original host persist and undergo proliferation has not been determined, although this seems possible. Animals with these cysts have not yet reached the age of the high frequency of cancer in rats, but it is interesting to speculate on the possibility of the cells of one individual under the stimulation of a specific parasite being able to grow, differentiate and undergo malignant transformation after transplantation to another individual of the same or another species.

B. M. FRIED.

THE BREAKDOWN OF HEREDITARY IMMUNITY TO A TRANSPLANTABLE TUMOR BY THE INTRODUCTION OF AN IRRITANT AGENT. ELIZABETH JONES, J. Cancer Research **10**:435, 1926.

Jones investigated the effect of an irritating agent in the production of susceptibility to an inoculable tumor in nonsusceptible strains of mice. As an irritant she used sterilized, nondyed, pure wool flannel. The experiments were conducted on black and albino mice. Both the black and the albino stocks have been used in numerous experiments as nonsusceptible controls. The animals were inoculated by the customary trocar method, the tissue being placed in the axillary region. The results obtained indicate a large percentage of positive results. On histologic examination and by inoculation of the "induced" tumors into different strains of susceptible and nonsusceptible mice, it was evident that growth of the original tumor has been induced through the presence of the flannel, and that the neoplasms are not growth of the tissue of the host.

B. M. FRIED.

A STUDY OF THE SUPPOSED MULTIPLE FACTORS IN CHICKEN SARCOMA. MAX CUTLER, J. Cancer Research **10**:450, 1926.

Gye attributed the infectivity of Rous chicken sarcoma to (1) a particulate body capable of cultivation, which he thought is probably a "virus" and (2) a labile chemical substance which renders the cells susceptible to infection by

the other agent. He stated that a tumor is produced only when these two substances are combined. Moreover, he asserted that certain mammary tumors possess an agent which is apparently identical with the supposed "virus" of the Rous chicken sarcoma. The study by Cutler was made under "the personal instruction of Dr. Gye." His experiments given in detail "do not permit him to confirm the presence of two factors in the Rous tumor filtrate."

B. M. Fried.

Effect of Host Immunity to a Filtrable Virus on a Transplantable Rabbit Neoplasm. Louise Pearce and Thomas M. Rivers, J. Exper. Med. **46**:65, 1927.

Rabbits were immunized with a filtrable virus (III) and then inoculated with transplantable tumor. The resulting growth was much less extensive than in normal animals, due, it is believed, to a nonspecific resistance.

Effect of Filtrable Virus on Transplantable Neoplasm of Rabbit. Louise Pearce and Thomas M. River, J. Exper. Med. **46**:81, 1927.

The more severe disease developed in the animals inoculated with tumor and virus than in the animals inoculated with tumor only. The influence of virus III on malignant disease is analyzed and discussed.

Diet and Cancer with Special Reference to the Incidence of Cancer Upon Members of Certain Religious Orders. S. Monckton Copeman and Major Greenwood, Reports on Public Health and Medical Subjects, no. 36, 1926.

A minute investigation of the vital statistics of a number of the houses of Catholic Religious Orders in England has not confirmed the conclusion of Russell that the incidence of fatal cancer on Cistercian and Carthusian monks is relatively much less than on the general population of males of like ages. This conclusion also applies to such other religious orders as were investigated and to both sexes. A wider survey, covering Cistercian houses all over the world, failed to confirm or refute the conclusions suggested by the smaller collection of English data; the general statistics were too incomplete to justify any conclusions. Judged by any available criterion, the recorded incidence of cancer was low, but a check on the accuracy of record was not possible, except in the case of one house in Belgium, the data of which, treated in the same way as the English data, led to a conclusion identical with that suggested by the English data.

Authors' Summary.

The Incidence of Intrathoracic Tumors in Manchester. J. B. Duguid, Lancet **2**:111, 1927.

In a total of 10,790 autopsies recorded at the Manchester Royal Infirmary from 1868 to 1926, 175 indisputable, primary, malignant intrathoracic tumors occurred. Material for histologic examination was available in only 78 and was divisible into two groups. The first included tumors known to arise from the bronchi; the large celled alveolar carcinoma occurred sixteen times at the average age of 51 years; the squamous cell type occurred thirteen times at the average age of 46 years. In the second group, the "oat-cell" tumor occurred thirty-two times at an average of 43 years; seven small round cell tumors that were exceptions to the ones generally seen and which were classed as pleural endotheliomas completed the list.

From 1868 to 1885, the percentage incidence was 0.24, whereas from 1921 to 1925, it was 2.57. The diagnosis was made in 0.9 per cent of 16,394 patients in hospital wards in the latter period. Males represented 86 per cent of the 175 patients, and three times as many tumors occurred in any five year period

between the ages of 36 to 60 years as at any other time. Workers on transports were affected three times as often as any other type, and it is suggested that a chronic catarrhal bronchitis may precede the malignant condition. Invasion of the pericardium, esophagus and superior vena cava occurred in the order named, and secondary growths occurred most frequently in the liver, abdominal lymph glands, suprarenals, kidneys and bone. The conclusions are: Bronchiogenic carcinomas comprise 80 per cent of the intrathoracic new growths, granting that the "oat-cell" tumors arise in the bronchi. Specific impurity has not been found in the Manchester air to account for the increase in such tumors, nor does the influenza epidemic of 1918 seem to assume the importance attributed to it on the continent of Europe.

GEORGE RUKSTINAT.

ACTION OF TUMOR EXTRACTS ON TISSUES IN VITRO. A. H. DREW, Brit. J. Exper. Path. **8**:176, 1927.

The results of Heaton, which showed that alcoholic yeast extracts may stimulate and inhibit tissue cultures, are confirmed. Alcoholic extracts of transplantable mouse tumors had no effect, while watery extracts varied in effect according to whether they were prepared from rapidly growing or receding tumors.

RADIUM CARCINOMA OF THE THUMB. C. P. G. WAKELEY, Brit. J. Surg. **14**: 677, 1927.

A typical squamous cell carcinoma developed in a man, aged 65, who had been handling radium salts for a number of years.

BENSON BLOOM.

THE METABOLISM OF CARBOHYDRATES OF CANCEROUS TISSUE. A. BLANCHETIÈRE, Bull. de l'assoc. franç. p. l'étude du cancer **16**:3, 1927.

Warburg observed that the respiration of the egg of a sea urchin increases six times as soon as it becomes fertilized. He wondered whether an analogous phenomenon is liable to occur in superior animals whose tissues passed from a resting into a state of active proliferation. By investigating in vitro Flexner-Jobling's rat cancer he noted, however, that the respiratory coefficient of the tumor tissue was much inferior to that of normal tissues. He attributed this to the glucose which acts as an inhibitory agent on the respiration by virtue of the accumulated lactic acid in the medium. Investigation has shown that normal tissue placed in analogous conditions furnishes only slight traces of this acid. It was then assumed that the high production of lactic acid is precisely the feature peculiar to neoplastic tissue. Warburg devised a method by the use of which he was able to determine in the tissue the "glycolytic coefficient." He stated that transformation of a normal respiratory type of respiration to a neoplastic type may occur in two ways: (1) By accelerating the glycolysis without a simultaneous acceleration of the respiration; (2) by inhibiting the respiration without simultaneous inhibition of the glycolysis. He was able to induce experimentally the second manner of respiration by (*a*) adding a certain dose of cyanide to chick embryo tissue which inhibited the respiration but which did not affect the glycolysis, thus obtaining a "malignant tumor type," and by (*b*) keeping anaerobically at body temperature the chick embryo tissue in Ringer's fluid for a few hours. Moreover, by transferring the tissue into an oxygenated milieu, its feeble respiration remained unchanged, and it was therefore unable to lead to a disappearance of the acid.

Here, then, the embryonic cell has undergone a profound change which Warburg attributed to "energism of growing tissues" analogous to the process of muscular energy described by Hill (Muscular Activity, 1926) and by Meyerhof (Chemical Dynamics of Life Phenomena, 1924). Warburg claimed that glycolysis in normal tissues is confined to certain cells only. In instances in which there is a persistent deficiency in oxygen, normal tissue is replaced by

an embryonic type of tissue which possesses a higher glycolytic activity, i. e., by neoplastic tissue. Numerous investigations along the same line are in accord with those of Warburg. Blanchetière investigated the glycolytic power of a rat sarcoma. He described his technic in detail. He did not agree entirely with the high figures given by Warburg, nor did he accept all Warburg's theories. He stated, however, that "the glycolytic phenomenon noted by O. Warburg appears to be perfectly well established."

B. M. FRIED.

CONCERNING TUMORS AMONG THE NONCIVILIZED BLACK RACE IN AFRICA. SURMONT and SAVA, Bull. de l'assoc. franç. p. l'étude du cancer **16**:136, 1927.

The documents published by Surmont and Sava concern African negroes "who are not only far from civilization but whose conditions of life remained primitive." The data are based on observations collected by French and Belgian physicians who lived for a long period of time in the equatorial region. Their conclusions are that "different kinds of malignant tumors can be found outside of civilized life." The authors urge a more detailed investigation of cancer of the stomach among African negroes, as its existence has been particularly denied.

B. M. FRIED.

THE RADIO RESISTANCE OF SKIN EPITHELIOMA PREVIOUSLY IRRADIATED. G. ROUSSY and SIMONE LABORDE, Bull. de l'assoc. franç. p. l'étude du cancer **16**:180, 1927.

Roussy and Laborde called attention to the fact that in certain cancers the sensitiveness to radium diminishes or ever disappears during the course of a successive irradation.

In the treatment of epithelioma of the skin, this phenomenon manifested itself in these ways. In one way the cancer was refractory to the roentgen-ray treatment from the beginning, although the technic was apparently correct. In the second way, the epithelioma became resistant following frequent but insufficient applications of the roentgen ray. Clinically, the aspect of these resistant ("vaccinated") cancers is that of an atonic, necrotic, painful ulcer. Pathologically, similar cancers do not appear to represent any peculiarities, although the stroma apparently plays some rôle.

B. M. FRIED.

TUMOR OF MESENTERY. H. OKA and S. MIYAIRI, Gann **21**:17, 1927.

The tumor caused an infrapapillary duodenal stenosis, and aroused the suspicion of being a carcinoma with metastases in the mesenteric lymph nodes. The microscopic appearance was that of a reticulo-endothelial tumor, resembling Komocki's sarcoma reticulare. The site of the primary tumor could not be determined.

FORMATION OF ANTIBODY AGAINST EXPERIMENTAL CARCINOMA IN MOUSE. K. YAMAGIWA, S. TSUKAHARA and S. MORIMOTO, Gann **17**:1, 1927.

Intravenous injection of extract of spleen of a guinea-pig that has been inoculated with an emulsion of mouse breast carcinoma has an inhibitory effect on the growth of a transplanted tumor. The effect of each injection is of about two weeks' duration.

RETROPERITONEAL TERATOMA. M. SEKI, Gann **17**:20, 1920.

The patient was 22 months old. The tumor was as large as an infant's head and cystic, arising from the inner aspect of the left anterior abdominal wall. It contained some cartilage and bone, but no teeth or hair. On microscopic examination the tissues were found to be fully developed embryonal layers, with anlage of the various organs and systems.

TWO CASES OF SYMPATHICOBLASTOMA. BENVENUTO CAPALDI, Frankfurt Ztschr. f. Path. **35**:83, 1927.

The author described two patients with sympathicoblastoma. The first case was in a woman, aged 44, who had a tumor in the spinal canal beside the seventh cervical and first thoracic vertebrae. Three weeks before death, she suddenly developed ischial pain and paresthesia of the lower extremities followed by paralysis of the lower half of the body. Shortly afterward, she developed a similar condition of the upper extremities. The condition was thought to be sarcoma of the spine or tuberculous spondylitis. The author interpreted the tumor as an undifferentiated sympathicoblastoma. The tumor was highly malignant, as shown by the rapid infiltrative growth and the presence of numerous mitoses.

The second case was in a girl, aged 2 years, who developed large nodular tumors in the region of the clavicles, each about the size of an apple. The tumors in this case were true expansive growths with nothing of the aggressive character of the first case. Clinically, they were thought to be metastases of the lymph nodes. The large tumor, however, was found to connect with small nodular primary growths in the spinal canal. Histologically, the tumor proved to be a well-differentiated sympathicoblastoma.

Capaldi remarked that the first case is an absolute opposition to the usual experience that unripe tumors of the sympathetic nervous system are found essentially in young persons. On the other hand, the tumor in case 2 is a rapidly differentiating one of the type usually described in the literature in a 2 year old child. Thus, both of the cases are in full opposition to the principle of Martius, "dass die Gewebsdifferenzierung des Tumorgewebes mit dem Alter des Geschwalstträgers zunimmt" and further "dass diese Tumoren mit Zunahme der Gewebsreife immer mehr den character der Malignitat verlieren."

E. M. HALL.

EARLY CHANGES IN EPITHELIOMA OF CERVIX UTERI. W. SCHILLER, Virchows Arch. f. path. Anat. **263**:279, 1927.

From a study of a number of cases of early carcinoma of the cervix, the author concludes that, histologically, transition stages from normal to carcinomatous cells cannot be recognized. In many cases in which the carcinoma had not advanced to the stage of invasion, a sharp line of demarcation could be found between cancerous and noncancerous epithelium. The presence of intranuclear and paranuclear vacuoles and red inclusions is a striking, but not pathognomonic, change observed in the epithelium adjacent to the carcinoma. These are considered degenerative phenomena, which also occur in other disease conditions of the uterus. The carcinoma advances, not by invasion of the normal epithelium, but by "assimilation," the acquisition by nonmalignant epithelium of carcinomatous characteristics. This change is considered to be a sudden one and is preceded by degenerative phenomena.

BENSON BLOOM.

PALISADE NUCLEAR ARRANGEMENT OF FIBROMYOMA OF UTERUS. W. SCHILLER, Virchows Arch. f. path. Anat. **263**:368, 1927.

The palisade arrangement of nuclei had been considered characteristic of neurinomas, but Schiller found it not uncommonly in fibromyomas, and he believed that such tumors arise from a single myoblast, producing such parallel rows of nuclei by amitotic division. The cells of the palisade tend to be arranged parallel to the blood vessels, but genetic relationship is not thought to exist between the blood vessels and fibromyomas.

BENSON BLOOM.

AUTOLYZING FERMENTS OF SARCOMA. W. VON GAZA and B. BRANDI, Virchows Arch. f. path. Anat. **263**:396, 1927.

Determinations of nitrogen were made on autolyzed sarcoma tissue to find the optimum p_H for autolysis. Three such values were found; 3.9, 8.6 and 6.4, indicating, respectively, the presence of a primary pepsin-like protease, a secondary trypsin-like protease, and the last representing a mean optimum p_H for all the proteases. The primary protease predominated, agreeing with the fact that collagen is affected by pepsin but not by trypsin. Because of its homogeneity, sarcoma tissue lends itself readily to determinations of its ferment content.

BENSON BLOOM.

KAPOSI'S SARCOMA MULTIPLEX PIGMENTOSUM. H. HAMDI and T. HALIL. Virchows Arch. f. path. Anat. **263**:404, 1927.

From a study of three cases, the authors believe that the nodules which characterize this condition arise from the perithelium of blood vessels. The hemangiomatous and lymphangiectatic nature is thought to be secondary to tears in the connective tissue, leaving spaces that are later lined by endothelium. The presence of iron pigment is not considered characteristic. The melanin of the epidermis is increased. The author agrees with other authors who maintain the infectious rather than the neoplastic character of the disease.

BENSON BLOOM.

EXPERIMENTAL TAR CANCER. C. BONNE, Ztschr. f. Krebsforsch. **25**:1, 1927.

From the results obtained in a large series of tar cancers in his laboratory, Bonne selected some data of general interest. The tar was applied twice weekly, and in the majority of mice the first lesion appeared after thirty applications. Epitheliomas develop after a smaller number of applications, but there is a latent period, the duration of which varies with the number of applications. Papilloma of the stomach was more frequent in mice who had received applications of tar than in controls. To prove that this greater frequency is due to the local action of swallowed tar, the material was applied about the mouth and nostrils in a series of mice; in such animals, the highest percentage of papilloma of the stomach was obtained. Carcinoma of the mouth developed in one mouse, and of the esophagus in two. Numerous epitheliomas of the lips developed in the mice of this series. Carcinoma of the lung was much more frequent in mice who had received applications of tar than in controls, but it was not possible to prove by the experimental inhalation of particles of tar that the greater incidence was due to a local action of the material. Rats were not as susceptible to tar cancer as mice. Although the usual site for the application of tar in rabbits is the ear, Bonne found it possible to produce metastasizing epitheliomas in this species by painting the skin of the back.

O. T. SCHULTZ.

PSEUDOPROTOZOAN PARASITE OF CARCINOMA. O. MACHIARULO, Ztschr. f. Krebsforsch. **25**:23, 1927.

Machiarulo concluded that the intracellular and extracellular bodies, which Joseph Koch recently described in carcinomatous tissues as protozoa, are degenerated cells and cell inclusions derived therefrom.

O. T. SCHULTZ.

CARCINOMA METASTASES IN THE SPLEEN. T. YOKOHATA, Ztschr. f. Krebsforsch. **25**:32, 1927.

By means of the Christeller method of microscopic sections of whole organs, Yokohata searched for metastases in the spleen of persons who had died from carcinoma. He examined only such spleens as did not contain gross secondary tumors. In previously published tabulations the incidence of metastasis to the

spleen is given as an average of 1.76 per cent, with a maximum of 4.3 per cent reported by Steinhaus. Yokohata studied the cases of twenty-nine patients with carcinoma and found microscopic metastases in ten (53 per cent). In four of these the metastases were limited to the hilum or capsule and were the result of direct extension. Of the remaining six patients with true metastasis, one was considered lymphogenous and the rest, hematogenous. Yokohata concluded that it is possible to find microscopic evidence of carcinoma metastasis to the spleen in a much higher percentage than reported. The small masses of tumor cells seen by him did not show evidence of degeneration, and he is unable to offer an explanation of the infrequency of macroscopic secondary tumors.

O. T. SCHULTZ.

INTRACUTANEOUS IMMUNIZATION OF RATS AGAINST TUMOR. E. KNOPF, Ztschr. f. Krebsforsch. **25**:64, 1927.

Knopf proposed the intracutaneous inoculation of small bits of carcinomatous tissue, which results in widespread dermatitis, as a method of treatment of carcinoma. In rats, he reported that the intracutaneous inoculation of a single small bit of tumor tissue protected the animals against later subcutaneous inoculations of the homologous neoplasm.

O. T. SCHULTZ.

HISTOLOGY OF BACILLOGENOUS RAT TUMORS. H. AULER, Ztschr. f. Krebsforsch. **25**:78, 1927.

The new growths of the tissues of rats, which follow the injection of certain bacteria and which Auler has described as blastomas, have been said by some to be granulomas. Auler attempted to meet this objection by the presentation of a number of photomicrographs and descriptions of the histologic structure. Because of the variation in the size of the cells and their nuclei and because of the invasiveness of the newly formed tissue, he concluded that his tumors are true blastomas, for which he accepts Pick's designation of malignant alveolar blastoma. However, he is unable to decide whether the tumor is of epithelial or endothelial origin.

O. T. SCHULTZ.

TISSUE CULTURES OF CARCINOMA. A. FISCHER, Ztschr. f. Krebsforsch. **25**:89, 1927.

The in vitro growth of pure strains of carcinoma cells has been difficult because of the rapid liquefaction of the medium by the cells. Fischer overcame this difficulty by adding to the medium small bits of killed embryonic or adult tissue. The tumor used was a strain of Ehrlich mouse carcinoma. In such cultures the tumor cells invaded the added tissue, and in this way it was possible to obtain a pure culture of carcinoma cells, the growth of which it was possible to continue for a long time. Contrary to the assertion of Rhoda Erdmann that explanted mouse carcinoma loses its ability to produce tumors when implanted into mice unless living stroma is also transplanted, Fischer found that cultivation of carcinoma cells in pure culture did not reduce their ability to lead to the formation of tumors when implanted into mice.

O. T. SCHULTZ.

PLANT TISSUE HYPERPLASIA DUE TO A FILTRABLE CULTURE DERIVATIVE. H. BECHOLD and L. SMITH, Ztschr. f. Krebsforsch. **25**:97, 1927.

In work with a bacillus isolated by Blumenthal and apparently identical with Erwin Smith's *B. tumefaciens,* the authors found that filtrates of the organism caused hyperplasia of plant tissue as well as did the organism itself. It was not possible to detect any ultramicroscopic particles in the filtrate. The material which leads to the tissue overgrowth is not a living agent, since it withstands boiling for twenty minutes and the action of 1 per cent phenol

for one hour. The authors concluded that the material is a finely dispersed hydrophil colloid, for which they propose the name tumefaciens-plastin, and that it is not to be placed in the group with the simple stimulants of the growth of plant tissue, such as lactic acid and certain inorganic salts.

O. T. SCHULTZ.

MENDELIAN HEREDITY OF TUMORS IN MAN. FRANCIS MICHE, Schweiz. med. Wchnschr. **57**:646, 1927.

By comparing statistics of malignant and benign tumors with the predictions that can be derived from mendelian rules, Miche concluded that the etiology of these tumors is purely hereditary and mendelian. Their incidence apparently corresponds to a social dihybridism with independent segregation and without lethal factors, which would modify the statistical relations.

AUTHOR'S SUMMARY.

CHANGES FROM PAINTING SKIN OF WHITE MICE WITH TAR. G. GULDBERG, Norsk. Mag. f. Lægevidensk. **88**:425, 1927.

Papillomatous growths, incipient carcinoma and carcinoma with metastasis were produced by painting white mice with tar. Myelogenous and amyloid degeneration as well as chronic interstitial nephritis also resulted. Tar was deposited in the interior of the tissues.

Medicolegal Pathology

REPORT OF A CASE OF FATAL METHYL SALICYLATE POISONING. J. B. PINCUS and H. E. HANDLEY, Bull. Johns Hopkins. Hosp. **41**:163, 1927.

A child, aged 22 months, swallowed a quantity of methyl salicylate, not more than 60 cc. Cyanosis, formation of acetone body and convulsions developed, and death resulted fourteen hours later. Autopsy was not obtained. Acidosis, retention of phosphates and chlorides, and increase in the nonprotein nitrogen were present.

THE "BLOOD GROUPS" IN LEGAL MEDICINE. R. DUJARRIC DE LA RIVIÈRE and N. KOSSOVITCH, Ann. de méd. lég. **7**:390, 1927.

In this review of the medicolegal applications of the study of blood grouping, the important relationship to questions of parentage is nicely emphasized. A brief chart, which indicates that with a mother of group A and a child of group B or AB, a father of group A is eliminated, and so on through the list of combinations, is followed by pointed examples of its use. A woman and the man whom she accused as the father of two of her children were both in group O. The children, belonging to groups A and B, respectively, could have inherited their agglutinogens only from their father (or fathers), so the man of group O could not be the parent. In the other case, the identification marks were lost from two infants born in a hospital to families M and P, respectively. The blood groups were found to be as follows:

Family M	*Family P*
Mother A	Mother B
Father A	Father A
Child A	Child B

Since the child of group B could belong only to family P, the child of group A, which otherwise could belong to either family so far as blood grouping could show, must in this instance belong to family M. Such a favorable case illustrates the positive aid that may be obtained from a knowledge of the blood grouping.

ETHEL B. PERRY.

RUPTURE OF THE HEART IN THE COURSE OF GANGRENOUS SEPTICEMIA FOLLOWING ACCIDENT TO THE HAND. E. SOREL, Ann. de méd. lég. **7**:461, 1927.

A man, aged 62, died suddenly while suffering from an extensive gangrene of the left hand and general septicemic symptoms. At the autopsy six weeks later, there was found a rupture of the left ventricle which was ascribed to acute myocardial degeneration caused by the septicemia. Disease in the aorta or coronary arteries was not present.

TRAUMATIC DIABETES FROM THE MEDICOLEGAL POINT. H. DURAND, Ann. de méd. lég. **7**:470, 1927.

The reasonably probable diagnosis of traumatic diabetes appears to be justified when true diabetes develops in a previously healthy person soon after definite injury to the head or the hepatopancreatic region.

POISONING BY LEAD-WATER (EAU BLANCHE) AND LOCALIZATION OF LEAD. C. VALLÉE and H. LEQUENNE, Ann. de méd. lég. **7**:479, 1927.

A man, aged 25, was poisoned fatally from being given in all 3 liters of lead-water mixed with milk. The following quantities of lead were obtained on analysis in each 100 Gm. of material:

	Gm.		Gm.
Beard	1.0246	Liver	0.0094
Teeth	0.0329	Kidney	0.0073
Bile	0.0166	Brain	0.0043
Tongue	0.0152	Lips	0.0024
Maxilla	0.0129	Lungs	0.0017
Intestines	0.0119	Abdominal muscles	0.0008
Heart	0.0111	Stomach	0.0051

CHEMISTRY OF FATS OF ADIPOCERE. S. GOY, Biochem. Ztschr. **187**:471, 1927.

Goy had previously had the opportunity to make a study of the chemical composition of the fats of adipocere obtained from two cadavers. In the present short article, he recapitulates his previous observations, adds those from a third case, and gives the results of a similar investigation of fresh human fat obtained at post mortem. The most marked change in adipocere, as compared with fresh normal human fat, is a marked increase in acidity due to free fatty acids. This is interpreted as evidence of splitting of fats, the glycerin disappearing because of its solubility. The iodine number is decreased, indicating a decrease in oleic acid. Whether this is due to hydrolysis or to the fact that the more fluid character of oleic acid at ordinary temperatures permits escape of the unsaturated acid, the author is unable to decide. Alterations in the fatty acid content of adipocere is indicated also by the high Reichert-Meissl numbers obtained.

O. T. SCHULTZ.

Technical

COMPARISON OF THE KAHN PRECIPITATION TEST, THE MEINICKE PRECIPITATION TEST, THE KOLMER-WASSERMANN TEST AND THE RUEDIGER-WASSERMANN TEST. E. H. RUEDIGER, Am. J. Syph. **11**:450, 1927.

Parallel Kahn precipitation tests, Meinicke precipitation tests, Kolmer-Wassermann tests and Ruediger-Wassermann tests were done on 265 consecutive specimens. Of these, 165 gave negative results by all four methods, and 100 gave positive results by one or more methods. Among those which gave negative results by all four methods were several specimens that came from patients who had been treated for syphilis and two specimens from patients with primary syphilis. Of the 100 specimens that gave positive results, fifty

gave positive results by all four methods and in forty-one the results did not agree. The Ruediger-Wassermann test gave positive results with all of these 100 specimens. As compared with the Ruediger-Wassermann test, the Kahn precipitation test missed 28 per cent; the Meinicke precipitation test missed 32 per cent, and the Kolmer-Wassermann test missed 30 per cent of the positives. The Kahn test gave positive results nine times when the Kolmer test gave negative results, and it gave positive results seven times when the Meinicke test gave negative results. The Meinicke test gave positive results three times when the Kahn test gave negative results, and it gave positive results four times when the Kolmer test gave negative results. The Kolmer test gave positive results with seven specimens that gave negative results by the Kahn test and with ten specimens that gave negative results by the Meinicke test.

AUTHOR'S SUMMARY.

THE SPECTROPHOTOMETRIC DETERMINATION OF HEMOGLOBIN. GEORGE E. DAVIS and CHARLES SHEARD, Arch. Int. Med. **40**:226 (Aug.) 1927.

Data obtained by various investigators clearly indicate that the Dare, the Sahli and the Tallqvist methods for the determination of hemoglobin are entirely too unreliable for use in making accurate determinations. The evidence concerning the method of Newcomer and that of Cohen and Smith is partly favorable and partly unfavorable. The object of the present work has been to investigate the possibilities of the spectrophotometric method. In each of fifteen different specimens of blood, the concentration of hemoglobin was determined by four different methods; namely, the van Slyke oxygen capacity, the spectrophotometric, the acid-hematin colorimetric (method of Cohen and Smith) and the Dare. In the spectrophotometric method, the hemoglobin was converted into oxyhemoglobin, and transmission readings were taken at a wave length of 542 millimicrons. A direct reading spectrophotometer was used, and results were obtained from a curve without computation. It was first necessary, however, to determine the absorption ratio A for oxyhemoglobin for a wave length of 542 millimicrons. The value of A, the absorption ratio, was found to be 0.001100 $\pm$ 0.000003. Forty-three independent determinations by the spectrophotometric method (no results discarded) gave values having an average variation of only 1.3 per cent from the van Slyke values, with a maximal variation of 3.3 per cent. The method, therefore, is shown to be highly accurate. Values given by the acid-hematin colorimetric method also agreed fairly well with the van Slyke values, differing on the average by 2.5 per cent, with a maximal difference of 7.7 per cent. The Dare method was highly inaccurate. This agrees with results by other experimenters. Readings by two different observers differed from the van Slyke readings by 8.8 and 17 per cent on the average, with maximal differences of 20.2 and 26.7 per cent. The authors concluded from their investigations that the spectrophotometric method of estimating hemoglobin is not only highly accurate but simple and fairly rapid as well. It should prove useful in diagnosis, in the work of standardization and in research. A simple and inexpensive form of spectrophotometer, with which a color filter and a neutral density wedge were used, has been tried out and found capable of giving fairly accurate results.

AUTHORS' SUMMARY.

TOTAL SUGAR OF BLOOD AND URINE. M. R. EVERETT, H. A. SHOEMAKER and F. SHEPPARD, J. Biol. Chem. **74**:739, 1927.

A method is described for the determination of total sugar in blood and urine filtrates. The experimental data, which serve as a basis for the method, are given. The data include glucose equivalents for known sugars and estimations of the destruction of sugar by acid and alkali.

AUTHORS' SUMMARY.

A New Spiral Streak Plate Method of Isolating Bacteria by Means of an Inoculating Machine. Philip L. Varney, J. Infect. Dis. **41**:190, 1927.

To overcome the difficulties and disadvantages inherent in present methods, a spiral streak method of isolating bacteria has been devised, which is performed by the aid of a new piece of apparatus called the "inoculating machine," a description of which is given. By the aid of this method petri dishes are rotated at a speed of from 200 to 400 revolutions per minute, while the inoculating needle is slowly drawn inward from the outer edge, hence a much longer line of inoculation is possible than by any of the hand methods now in use. A much greater pressure may be applied to the surface of the medium than by hand methods, and as a result of the greater friction so produced, a much more efficient breaking up or grinding of the inoculum is obtained than by hand streaking. The method may be used either for isolating bacteria, in which case a nichrome spud is used, or for producing heavy growths of bacteria for the preparation of antigens, in which case a nichrome loop is used. The method is rapid, simple and easy in operation.

Author's Summary.

Preservation of Virus of Herpes. J. R. Rerdrau, Brit. J. Exper. Path. **8**:167, 1927.

The brain is covered with a volume — not greater than its own — of either pure neutral glycerin or glycerin diluted with an equal quantity of salt solution; then a column of liquid paraffin, about 1 inch (2.5 cm.) deep, is floated on top. The material is placed in cold storage, and the glycerin is not changed. There was no obvious falling off of the infectivity of infected brains after twelve months.

Staining Properties of Pseudomelanotic Granules. A. Fabris, Arch. per le sc. méd. **49**:99, 1927.

The author studied the slate-colored pigmentation that develops in old hemorrhagic foci during putrefaction. It is due to the action of sulphids on hemosiderin. He found that such granules accept the basic aniline dyes, such as methylene blue. This property of the granules may mislead to a diagnosis of mast cells instead of histiocytes containing pseudomelanin granules, especially in examination of serous membranes. On the other hand, it is possible to differentiate easily the pseudomelanotic pigment from the melanotic (non-hematogenous and from anthracosis), since these pigments are not affected by the stain. The method may also serve for demonstration of iron in the tissues after preliminary treatment with ammonium sulphid.

K. Schulhof.

A New Method for the Demonstration of Urochromogen in Urine. E. Schuntermann, Beitr. z. klin. d. Tuberk. **65**:773, 1927.

To a few granules of sodium perborate, a sufficient amount of concentrated ammonia-free sulphuric acid is added to dissolve it. After cooling, 1 cc. of this solution is mixed with a double amount of urine; after cooling again, 3 cc. of ether is added and the mixture is shaken. The reaction is positive if the ether extract assumes an intensive lemon yellow color which fades in a short while. Slight discolorations of the ether occur with normal urines.

Max Pinner.

Turbidity and Microreactions of Meinecke Test in Comparison with the Wassermann and the Sachs-Georgi Reactions. M. Stern and T. Frank, Klin. Wchnschr. **6**:254, 1927.

The four tests named were performed on the serum of 2,000 patients with syphilis in all stages, tuberculosis, dermatitis, gonorrhea and lupus. There

was complete agreement in 91.5 per cent of the tests, and variation in the rest. The percentage of positive reactions was greater with any combination of any two of the reactions than with any single test. The Wassermann reaction with the Meinecke turbidity test gave the greatest percentage of positive reactions.

J. D. WILLEMS.

A NEW OXYDATION REACTION OF THE CEREBROSPINAL FLUID. L. BENEDEK and E. VON THURZÓ, Klin. Wchnschr. **6**:356, 1927.

The performance of a new, simple oxydation reaction of the cerebrospinal fluid with oxalic acid and potassium permanganate requires eight minutes. The test is diagnostically reliable in general paralysis, taboparesis, cerebrospinal syphilis and meningitis.

J. D. WILLEMS.

THE BIOLOGIC DIAGNOSIS OF ACTIVE PULMONARY TUBERCULOSIS WITH SPECIAL REFERENCE TO TEBEPROTIN AND TO THE SEDIMENTATION REACTION. M. LAUTERBACH, Ztschr. f. Tuberk. **47**:301, 1927.

The sedimentation rate in the same patient on two subsequent days may vary 10.9 per cent in the average, with a maximum variation of more than 30 per cent. If the sedimentation rate increases more than 30 per cent after the injection of 0.001 mg. of tebeprotin, the presence of an active tuberculosis is probable, but the clinical symptoms must always be considered. Tebeprotin in equal doses does not produce a marked change in the sedimentation reaction in nontuberculous patients.

MAX PINNER.

THE QUESTION OF MEDIUMS FOR TUBERCLE BACILLI. R. MELLER, Ztschr. f. Tuberk. **48**:137, 1927.

Different egg and potato mediums were compared in regard to their adaptability for the isolation of tubercle bacilli according to Löwenstein's method, and in regard to their efficiency for subsequent cultures. The growth on egg mediums was more abundant and sometimes faster; the isolation on potato mediums was more frequently successful than on egg mediums. The quality of the potato mediums showed seasonal variation. Slightly alkaline glycerin potatoes gave better results than nonalkalinized ones.

MAX PINNER.

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, Oct. 13, 1927

EUGENE L. OPIE, *Presiding*

CHRONIC LYMPHATIC LEUKEMIA WITH ALEUKEMIC BLOOD PICTURE. BAXTER L. CRAWFORD and EDWARD WEISS.

G. I. B., a white man, a painter, aged 55, was admitted to the Jefferson Hospital on May 4, 1927, and died on May 16, 1927. The chief complaints were: weakness, swelling of the legs and vague pains in the back and in the abdomen. The family history was negative. The patient's health had been generally fair. He had had diphtheria at the age of 18, and frequent sore throats during his youth, but no other serious illnesses. For the past year the patient had been unable to work regularly because of weakness, shortness of breath on exertion, and progressive swelling of the legs during the last month. An operation for hemorrhoids was performed in 1922. Nocturia occurred once daily. There was no evidence of a venereal disease. The patient had been married at the age of 25 and had five children who were living and well. He had had joint pains for several years, which lasted only a day or two.

The patient was a pale, white man, without cyanosis; clubbing was not present. The pupils reacted to light and were equal; there was slight infection of the gums, but no blue line; the throat was normal. The superficial lymph nodes were not enlarged. The heart was possibly slightly enlarged or pushed to the left. A systolic murmur was heard at the apex. The abdomen was asymmetric. The spleen was tremendously enlarged and firm and extended into the pelvis. The liver was enlarged and firm and extended to the level of the umbilicus. There was no apparent fluid.

On May 12, 1927, the patient developed fever, sore throat and pains in the joints. He became comatose and died on May 16, 1927. The blood count on May 5, revealed: hemoglobin, 60 per cent; red blood cells, 3,200,000; white blood cells, 8,900; the differential count showed: 22 polymorphonuclears, 1 eosinophil, 77 mononuclears and the white blood cells varied between 8,900 and 10,900. The blood platelets numbered 260,000. Coagulation time was two minutes and fifteen seconds; the bleeding time was one minute. The reaction to the van den Bergh test was negative. The blood Wassermann reaction was negative. The blood urea on May 12 was 58 mg. Fragility began at 0.38 and was completed at 0.26. The blood culture was sterile.

Repeated blood counts were made during the patient's stay in the hospital, and the highest total leukocyte count was 10,900 with an increase in the mononuclears varying from 70 to 80 per cent, the large majority of which seemed to be normal lymphocytes. Definitely pathologic cells were not found in the smears. The oxydase reaction failed to show the presence of granules in any of the mononuclear cells.

Autopsy was performed one hour and twenty minutes post mortem. The liver, which weighed 2,710 Gm.; the spleen, which weighed 1,860 Gm., and the mesenteric lymph nodes were markedly enlarged. The cut surface of both the liver and the spleen presented innumerable small, gray foci, the size of pin points, scattered uniformly throughout the substance. The lymph nodes were fairly firm and discreet; the capsules were intact. There were numerous small, circumscribed gray nodules on the serous surface of the stomach and small

intestine and numerous elevated circumscribed nodules on the mucous surface of the small intestine, principally confined to the Peyer's patches. A few small hemorrhages were present beneath the peritoneum and pericardium and in the lung. Microscopic examination of the sections from the lymph nodes and spleen showed extensive focal and diffuse infiltration by mononuclear cells, which closely resembled the normal lymphoid cell. There was also infiltration of the liver, lungs, kidneys and suprarenals by similar cells. Many of the foci of the liver closely resembled lymph follicles. The nodules in both the serous and mucous surfaces of the intestine were composed of masses of lymphoid cells. Section from the bone marrow, taken from the femur, did not show any histologic evidence of hyperplasia. The diagnosis was chronic lymphatic leukemia.

HISTOLOGIC DIFFERENCE BETWEEN A PRIMARY TUMOR AND ITS METASTASIS. JOSEPH MCFARLAND.

Two years ago, Mrs. M. L. R., white, aged 27, mother of two children, injured the right great toe. On examining it, an abrasion was found on the inner side near the metatarsophalangeal joint, and with it was a dark area that she called a "blood blister." The latter did not disappear, and was later treated by her medical adviser with ultraviolet rays and by fulguration, but it grew larger until at present it is about the size of a silver dollar; it is papular and slightly discolored from the alternation of scar tissue with telangiectasic areas.

About two months ago, she noticed a swelling in the right groin. It was painless, movable and without discoloration, but it grew steadily until it reached the size of an orange. The mass lies in Scarpa's triangle, close to the femoral side of Pourpart's ligament, which it partly covers. There was no edema of the thigh or leg, and there were no other tumors or enlargements of the lymphatic nodes. Roentgen-ray examination of the chest failed to reveal anything of interest. The spleen and liver seemed to be normal.

At the operation for its surgical removal, the mass was found to be a tumor, seemingly confined in a capsule, and without infiltration of the surrounding tissue. The internal saphenous vein was densely connected with the capsule and was resected, as were also the circumflex iliac vessels and some branches of the anterior crural nerve.

Microscopic examination of the lesion on the toe revealed the usual appearance of a nevus, and led to the supposition that a small lesion of that nature had probably existed for a long time without the patient's having been made aware of it until the accident called attention to it, or until the injury determined its rapid and malignant growth. It was then treated energetically, but without avail.

The lesion in the groin was found to be a metastasis, almost entirely without pigment, and with a structure so dissimilar from that of the primary tumor as to lead every one of six pathologists who examined it to make a diagnosis of sarcoma, without question whether it was primary or secondary. It was composed of large spindle cells with large pycnotic nuclei, and penetrated by blood vessels of the most striking immaturity, although some of them were large. In a general way, they had no walls. Only on most painstaking search was it possible to find a few groups of cells containing melanin.

The chief interest of the specimens lies in the fact that had nothing but the secondary tumor been at hand, it would probably never have been realized that it was not, itself, a primary spindle cell sarcoma of the groin. The invasion of the lymph node was so complete, and the necrosis of all but the newest portions of the tumor so pronounced that no one was able to recognize that the mass had probably originated in a lymph node.

VITILIGO ASSOCIATED WITH MULTIPLE SUBCUTANEOUS TUMORS, PROBABLY MELANOTIC. FRED D. WEIDMAN.

A colored man, aged 35, developed a classic vitiligo one and one-half years before presentation. Six months ago, he noticed a lump on the sole, which he said had developed from a "black scar" present since boyhood. Three months ago, multiple subcutaneous tumors made their appearance. At present, there are more than thirty spheroidal subcutaneous tumors, ranging in size from 3 to 4 cm. in diameter, distributed over the arms, shoulders and elsewhere on the trunk, but sparing the face and lower extremities. Only one is suggestive of being melanotic; that is the one which the patient says was the first to appear. The pigment is jet black and appears to affect the skin at the summit of the tumor and scarcely to be extending into the latter. The tumor on the sole is 3 or 4 cm. in diameter, not pigmented, but exhibits a highly projecting fungous growth, more or less covered by slough. In the last two or three days, a minute nodule has developed within the mouth. Roentgen-ray examination of the chest and bones did not reveal any neoplasms, and there are neither subjective nor objective symptoms or physical signs of visceral neoplasm.

The diagnosis of melanotic carcinoma was given in view of the history and the fact that the foot is the commonest site for cutaneous melanomas. The puzzling feature of the case is the absence of pigment in the tumors and the corresponding loss of pigment in the skin. It appears that there is an incapacity on the part of this patient to elaborate melanin not only affecting the skin, but extending to the neoplasm.

THE SURFACE OF THE TUBERCLE BACILLUS AND THE MECHANISM OF ITS REACTION WITH IMMUNE SERUM. STUART MUDD.

Serologic study of the immunity of animals to bacteria or other foreign cells has been largely concerned with the end-effects of certain reactions. Thus we observe clumping, solution or phagocytosis of our test cells and speak correspondingly of agglutinins, lysins or opsonins. While this type of study has been fruitful, it yields little information concerning the mechanism by which the immune serums bring about the observed results.

It has seemed highly desirable, then, to seek more direct methods for determining how the antigen cells are altered by their interaction with anti-serums. Two methods of observing directly the properties of the cell surfaces and the changes induced in them by immune serums have been described: (1) study of the electric charge by cataphoresis (Northrop, J. H., and De Kruif, P. H.: J. General Physiol. **4**:655, 1921-1922. Northrop, J. H., and Freund, J.: ibid. **6**:603, 1924. Shibley, G. S.: J. Exper Med. **40**:457, 1924; **44**:674, 1926. Falk, I. S., and Jacobson, M. A.: J. Infect. Dis. **38**:182, 1926), and (2) study of the wetting properties (Mudd, S., and Mudd, E. B. H.: J. Exper. Med. **40**:633, 1924; **43**:127, 1926; Biochem. Ztschr. **186**:378, 1927).

Applied to unsensitized acid-fast bacteria the cataphoresis method has shown the presense of protein in the surface (Freund, J.: Am. Rev. Tuberc. **12**:124, 1925), and the wetting method has shown the presence of lipin. After sensitization with serum, the acid-fast bacteria show markedly altered surface properties (Mudd, S., and Mudd, E. B. H.: J. Exper. Med. **46**:167, 173, 1927). These changes are produced specifically in the usual serologic sense; they parallel the binding of agglutinin by the bacteria.

The wetting properties of maximally sensitized acid-fast bacteria are indistinguishable from those of heat-denatured serum globulins. From cataphoresis and other data, Shibley (J. Exper. Med. **44**:667, 1926) has proposed that sensitized bacteria are coated with a film of denatured globulin. Our data therefore strengthen Shibley's important hypothesis.

OBSERVATIONS ON CERTAIN HYPERPLASTIC AND NEOPLASTIC PROCESSES AS THEY OCCUR IN THE SKIN. FRED D. WEIDMAN.

In every organic system, there are differences in embryology, anatomy and physiology which determine peculiarities of morphology when hyperplastic changes are induced in their tissues. These are so numerous, so varied in their shadings and clinical significance that they cannot well be gathered into any general descriptive groups, such as are arranged in general pathology; there is still need for a consideration of disease processes under the headings of both general and special pathology. The following citations pertain to certain hyperplastic and neoplastic phases of cutaneous disease processes. The microscopic change is the phase particularly referred to in the following.

1. The skin is particularly favorable for the study of the life history of congenital anomalies (nevi) because their growth can be followed by the eye and otherwise from the very beginning. Pigmented nevi which are known to be benign clinically may appear carcinomatous as judged by general pathologic criteria. Anomalies of the sweat glands and hair follicles may likewise take on carcinomatous appearances histologically, such as have long been known as benign cystic epithelioma.

2. The human epiderm has the capacity (developed perhaps phylogenetically) to regenerate to such a degree as to simulate cancer, morphologically. In the presence of known chronic cutaneous defects, the significance of epithelioma-like hyperplasias should be heavily discounted. Deep permeation, below the level of the sweat glands, is the only certain histologic criterion in some cases.

3. Sweat duct epithelium readily becomes hyperplastic in connection with suppurative and other irritative processes. It may be sufficiently irregular to suggest carcinomatous change.

The secretory portions of the sweat glands are singularly exempt from hyperplastic tendencies, even when surrounded by pus and when the ductal epithelium is hyperplastic. Neoplasia is excessively rare.

4. Rarely do the sebaceous glands become neoplastic. They are said to become hyperplastic in rosacea and seborrheic states, but it is difficult to separate hyperplasia from overdistention and overactivity in these states. A genuine hyperplasia occurs in a few chronic conditions, in which case *Demodex folliculorum* is likely to be associated. The relation of cause to effect in the latter connection is not established; the door is still open either way.

In the case of the skin, its accessibility to direct observation has helped the physician to diagnose the condition in several diseases; without this and with an eye only to the microscopic change, an entirely erroneous opinion would have been held. The skin is therefore recommended as a field to be more extensively used in experimental medicine.

Book Reviews

THE PRINCIPLES OF PATHOLOGY. By CHARLES POWELL WHITE, M.D., F.R.C.S., Honorary Lecturer in Pathology and Director of the Helen Swindells Laboratory in the University of Manchester. Price, $6. Pp. 279. University of Manchester Press, 1927.

This volume of 278 pages is correctly named "The Principles of Pathology." The arrangement of material and the manner of discussion are quite different from those of the usual textbook of pathology. The author is not concerned with a mere cataloguing of facts: he has attempted to formulate a sort of philosophy of pathology, and uses facts rather for purposes of illustration and as a basis of theory. The background of the discussion is a large panorama of science — chemistry, physics, zoology, general biology and even astronomy and geology.

Any attempt at philosophy which is not to end in confusion must be guarded by carefully worded definitions, and the terms defined must always be used in the same sense. One of the most valuable features of the book is the clear concise definitions with which it abounds. The discussion of each subject is prefaced by definitions of the terms to be used. These definitions do not have a dry, dictionary-like flavor. They are so well seasoned with illustrative material and discussion of facts that they do not offend by their abruptness and disconnectedness, but add much to the pleasure of reading the pages. For example, after elaborating the view that there is no living substance as such, but only living things, the author lists with brief discussion those phenomena which are characteristic of living things, selecting those which are truly differential, and then defines life as "a name which when predicated of any thing signifies the possession of capacity for growth, maintenance or assimilation."

The book is divided into three parts. Part I is introductory and deals with such subjects as "Pathology and Its Relationships" and "Morphological Structure of the Organism," including a discussion of many facts of general biology, chemistry and physics with special reference to their relation to pathology. All biologic phenomena, both normal and pathologic, are divided into the biostatic, including the conditions present in the organism at any one time; and the biodynamic, which comprise the changes that take place in the organism. The author is insistent that "the ultimate basis of life is a morphologic and not a chemical one. All living things and the parts of which they are composed have a definite morphological organized structure." Only organized structures, and not mere chemical substances, function. He elaborates three "fundamental principles of pathology" — growth, variation and adaptation — and, as a corollary to these, the further principle that "changes in the environment to which the organism is not adapted act injuriously upon it." The last chapter in part I deals with nomenclature and classification, and contains a helpful list of the chief prefixes, suffixes and root words used in expressing pathologic processes and conditions, with their meanings and examples of the use of each.

Part II is concerned with the "Causation of Disease." "The cause of any phenomenon is the immediate, invariable, unconditional and indispensable antecedent of the phenomenon." "It is a mistake to apply the term 'cause' to a material object or condition. It should only be applied to an action." The various causes of disease are grouped under two main classes: extrinsic and intrinsic causal factors. Avoidance of a commonplace discussion of the causes of disease is attained by adhering to the principle just quoted.

Part III deals with "The Processes of Disease." These are divided into: (1) consecutive processes, which are the direct effect of injury, and include mechanical, physical, chemical and functional processes, discussed from a fresh

and unusual point of view; (2) adaptive processes, which represent a reaction against the consecutive processes, and are concerned with adaptation and protective mechanisms, regeneration, inflammation and immunity, and (3) autonomous processes, which are independent of antecedent injury which may or may not have been present, and include malformations, atrophy and hypertrophy, and tumors.

The author admits that this "book is intended as an expression of personal opinion." This fact is evident on almost every page and is the source of both the faults and the charm of the book as a whole. The author has given much serious thought and well ballasted speculation to problems of pathology. He defends the conceded dogmatism of the book on the ground that "a positive or dogmatic statement has the advantage that it arrests the attention of the reader and provokes criticism whereas a hesitating non-committal statement is apt to be passed over as of no account." Although dogmatic, the clearness of the author's style usually leaves no doubt as to the meaning intended. Only now and then does he indulge in language that is not truly scientific. For instance, neurasthenia is defined as "a condition characterized by weak nerve power," a statement that means little.

"This book is not intended as a textbook on pathology. It is designed rather to supplement the textbooks and to draw attention to an aspect of General Pathology which is too much neglected in ordinary books, namely the biological and scientific aspect." This statement in the preface accurately and succinctly describes the book. It can be recommended to pathologists, general practitioners and medical students as a short and stimulating volume.

TEXTBOOK OF BACTERIOLOGY. By WILLIAM W. FORD, M.D., Professor of Bacteriology, School of Hygiene and Public Health; Lecturer on Hygiene, School of Medicine, Johns Hopkins University. Cloth. Price, $8.50, net. Pp. 1,069, with 186 illustrations. Philadelphia and London: W. B. Saunders Company, 1927.

This book, as stated by the author in his preface, is intended primarily for the medical student and the medical bacteriologist. Nearly thirty years devoted to bacteriologic research and to teaching bacteriology to medical students has specially fitted the author for the task which he has performed in a satisfactory manner. Long contact with hospital material and special interest in questions of hygiene have enabled him to make a judicious selection of material for presentation.

Part 1, including 181 pages, consists of a discussion of general bacteriology, including a historical introduction, morphology of bacteria, bacterioscopic methods, vital activities of the bacteria, methods of cultivation and distribution of bacteria and taxonomy. This part contains enough detail to answer most of the questions which arise in the minds of students. The thoroughness with which nutrient mediums and staining methods are presented will be appreciated by any one who has had occasion to search for them through scattered publications.

Part 2 deals with systematic bacteriology, and occupies about 600 pages. Special emphasis has been placed on the pathogenic organisms responsible for diseases in man and animals. The anaerobic bacteria are presented at some length, and aerobic sporulating species which specially interest the hygienist are included. This part represents a vast amount of labor, extending over many years, both in a study of published descriptions and in personal study in the laboratory.

Part 3 is a consideration of the distribution of bacteria, and in part 4 about 100 pages are devoted to a brief, intelligent presentation of the topic of infection and immunity.

Spirochetes, which have come to be of such great interest of late years, are satisfactorily discussed in part 5.

The final section is devoted to a discussion of the infectious micro-organisms of undetermined character, including the filterable viruses.

The illustrations for bacteria have been made from drawings and are much better and give more detail than photographs which are often most unsatisfactory. Throughout the book there are abundant references to the literature, which are a great convenience, and which, unfortunately, are so often omitted from textbooks.

It is safe to predict a long and wide usefulness for this book, both as a textbook for students and as a reference book for laboratory workers. It is not likely that another author will soon perform the arduous labor required to produce a book which will supplant this one.

HANDBUCH DER BIOLOGISCHEN ARBEITSMETHODEN. Herausgegeben von Geh. Med.-Rat PROF. DR. EMIL ABDERHALDEN, Direktor des physiologischen Instituts der Universitaet Halle a. d. Saale. Abt. VIII. Methoden der experimentellen morphologischen Forschung, Teil 1, Heft 6, Technik der Obduktion mit Einschluss der Massmethoden an Leichenorganen. Von ROBERT ROESSLE. Lieferung 226. Price, 9.60 marks, with paper cover. Pp. 1093-1246, with 39 illustrations. Berlin: Urban & Schwarzenberg, 1927.

The usual preliminary account of the aims of postmortem examinations, the necessary instruments, material, equipment and rooms is followed by directions for superficial incisions, illustrated by diagrams; these are followed by instructions for examinations of the various cavities and viscera of the body. In the general plan and in these particulars, this "Sectionstechnik" does not possess any noteworthy departures from many other similar works in any one of several languages. Following these, however, or inserted as addenda to the directions for examination of both separate regions and organs, other methods are explained, methods developed and reported by different masters of postmortem technic and more or less widely known. The Meynert, Rokitansky-Chiari and Pitre methods of sectioning the brain; the several ways of examining the abdominal viscera advocated by Virchow, Albrecht, Nauwerek, B. Fischer and others; the order of examining the interior of the entire body recommended by Ghon and the method sometimes referred to as the Letulle method are examples of the supplementary methods, which are carefully and briefly described. Directions for examination of the accessory nasal cavities and base of the skull are clear and impressive, also those for removal of the spinal cord from in front. A similar precise account of the methods of examination of all the organs of the trunk from behind after removal of the spinal cord and spine, with suitable illustrations and with an enumeration of the advantages that approach has for study of some diseases and their sequelae, would be a happy addition to the rich diversity Roessle has assembled.

Apparently the routine used by Roessle and his assistants at Basel is that most in vogue. It is a stimulating innovation in works of this character to have so many variations from the usual type set forth; the author is evidently familiar with all of them. The excellent bibliography at the end of the book has more than one hundred references to publications dealing with methods of postmortem examination. Another conspicuous asset of this work is in the directions for measurements made during, or subsequent to, necropsy, such as measurement of the cranial capacity and of the specific weight and volume of organs. There are helpful illustrations of apparatus for these procedures. Suggestions are also given for prudent measures to be taken and special adjustments of methods to suit the conditions when death follows accident, poisoning, surgical operations or certain diseases, such as miliary tuberculosis or embolism. That a technical exposition of postmortem examinations would be included in the Abderhalden handbook of biologic methods has been expected. The problem of adding another account with special merits to the many other excellent similar accounts already at hand has been well met.

RECENT ADVANCES IN HEMATOLOGY. By A. PINEY, M.D., M.R.C.P., Research Pathologist, Cancer Hospital, London. Price, $3.50. Cloth. Pp. 276, with 4 colored plates and 18 text figures. Philadelphia: P. Blakiston's Son & Co., 1927.

This book will be useful to those interested in hematology. As the author's interpretation of the various blood pictures differs from that of many accepted authorities, close students will disagree with some of his views; however, all will appreciate his comprehensive survey of the recent literature and the extensive bibliographies at the end of the chapters and in the appendix.

Practitioners will find a clear summing up of recent data on hematologic problems. At some points, space devoted to defense of the author's personal theories of the genesis of blood diseases might better be devoted to more detailed presentation of the simple facts.

The author takes the view that constitutional anomalies of hematopoietic tissues, some morphologically demonstrable and others manifested only by peculiar reactions to stimuli, are important factors in the origin of diseases of the blood. Stimuli such as bacterial invasion or metabolic changes, e. g., pregnancy, are capable of initiating abnormal hematopoiesis in congenitally predisposed persons. In livers from patients with pernicious anemia, small islands of megaloblastic tissue, which the author regards as embryonal rests of entodermal origin, are always demonstrable. Patients with this abnormality also have defects in the normal myelogenous tissue which forms red cells. The noxious agent that renders this tissue functionally impotent at the same time stimulates the embryonal islands of the liver to the production of megaloblasts. Imperfect formation of the gastric mucosa and of certain elements of the spinal cord are frequently associated anomalies in the "pernicious anemia constitution."

Leukemias, which the author prefers to designate myelosis or lymphadenosis, according to which type of white cell predominates in the blood, are regarded as neoplasias because of the microscopic appearance of the bone marrow in these cases. Infiltrations composed exclusively of one type of atypical blood cell are always found. These foci, in addition to producing the one type of white cell to which they can give rise, irritate the surrounding myeloid tissue to increased hematopoiesis. Thus, though several types of cells may be increased in the circulating blood, only one type participates in the new growths.

Hodgkin's disease is regarded as "aleukemic reticulo-endotheliosis."

Books Received

REAGENZIEN UND NÄHRBÖDEN. Eine Zusammenstellung der wichtigsten und zweckmässigsten Vorschriften für die Laboratoriumspraxis. Von Dr. Phil. E. Böhm und Dr. Phil. K. R. Dietrich. Price, 18 marks. Pp. 375. Berlin and Vienna: Urban & Schwarzenberg, 1927.

HOST-PARASITE RELATIONS BETWEEN MAN AND HIS INTESTINAL PROTOZOA. By Robert Hegner, Professor of Protozoology in the School of Hygiene and Public Health of the Johns Hopkins University. Price, $3.50. Pp. 231. New York and London: The Century Company, 1927.

CLINICAL DIAGNOSIS BY LABORATORY METHODS. A Working Manual of Clinical Pathology. By James Campbell Todd, Ph.B., M.D., Professor of Clinical Pathology, University of Colorado, and Arthur H. Sanford, M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation); Head of Section on Clinical Laboratory, Mayo Clinic. Ed. 6. Revised and Reset. Cloth. Price, $6. Pp. 748, with 346 illustrations, 29 in colors. Philadelphia and London: W. B. Saunders Company, 1927.

A TEXT-BOOK OF PATHOLOGY. By FRANCIS DELAFIELD, M.D., LL.D., Sometime Professor of the Practice of Medicine, College of Physicians and Surgeons, Columbia University, New York, and T. MITCHELL PRUDDEN, M.D., LL.D., Sometime Professor of Pathology, College of Physicians and Surgeons, Columbia University, New York. Fourteenth Edition. Revised by Francis Carter Wood, M.D., Director of the Pathological Department, St. Lukes Hospital, Director of the Institute of Cancer Research, Columbia University, New York. Price, $10.00. Pp. 1339, with 20 full-page plates and 830 illustrations in the text in black and colors. New York: William Wood & Co., 1927.

A review of the thirteenth edition and a summary of the history of this standard book are given in ARCHIVES OF PATHOLOGY **1**:496 (March) 1926.

THE RISE AND FALL OF DISEASE IN ILLINOIS. By ISAAC D. RAWLINGS, M.S., M.D., in collaboration with WILLIAM A. EVANS, M.D., D.P.H.; GOTTFRIED KOEHLER, M.D., and BAXTER K. RICHARDSON, A.B. Published by The State Department of Public Health in commemoration of its fiftieth anniversary, 1927. Illustrated with graphs developed and drawn by A. F. Dappert, and with picture reproductions of many persons associated in one way or another with the story. Indexed by Clara Breen. In two parts.

MODERN ASPECTS OF THE DIAGNOSIS, CLASSIFICATION AND TREATMENT OF TUBERCULOSIS. By J. ARTHUR MYERS, Associate Professor of Preventive Medicine, Medical and Graduate Schools, University of Minnesota. With an Introduction by David A. Stewart, Associate Professor of Medicine, Manitoba University. Pp. 265, 6 by 9, with 27 halftones and 7 line cuts. Price, $5.50. Baltimore: The Williams & Wilkins Company, 1927.

DIE WICHTIGSTEN KRANKHEITEN DES KANINSCHENS MIT BESONDERER BERÜCKSICHTIGUNG DER INFEKTIONS- UND INVASIONSKRANKHEITEN VON PRIVATDOZENT DR. OSKAR SEIFRIED, Abteilungsvorsteher am Veterinärhygienischen- und Tiereuchen- Institut der Universität Giessen. Mit 54 Abbildungen im Text. Pp. 160. Price, 15 marks. München: Verlag von J. F. Bergmann, 1927.

MIKROMETHODEN ZUR BLUTUNTERSUCHUNG, IVAR BANG BEARBEITET VON GUNNAR BLIX. SECHSTE DURCHGESEHENE UND VERBESSERTE AUFLAGE. MIT 7 ABBILDUNGEN IM TEXT. Price, marks 4.20. Munchen: Verlag von J. F. Bergmann, 1927.

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